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File 410:Chronolog(R)  1981-2000 Sep/Oct
       (c) 2000 The Dialog Corporation plc

      Set  Items  Description
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HILIGHT set on as ''
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            $0.00    0.058 DialUnits File410
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     $0.10  TYMNET
     $0.10  Estimated cost this search
     $0.11  Estimated total session cost   0.228 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-2000/Dec W4
         (c) format only 2000 Dialog Corporation
*File 155: For information on updating, changes to the file, and
check tags information please see Help News155.
  File   5:Biosis Previews(R)  1969-2000/Nov W4
         (c) 2000 BIOSIS
  File  72:EMBASE  1993-2000/Oct W4
         (c) 2000 Elsevier Science B.V.
*File  72: Update codes are currently undergoing readjustment.
For details type Help News72.
  File 442:AMA  Journals  1982-2000/Oct B2
         (c)2000 Amer Med Assn -FARS/DARS apply
*File 442: There is no data missing. UDs have been adjusted to reflect
the current months data. See Help News442 for details.

      Set  Items  Description
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            1218  GLUTAMIC ACID DECARBOXYLASE
      S1      12  PARKINSON? AND GLUTAMIC ACID DECARBOXYLASE
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...completed examining records
      S2      12  RD (unique items)
? t s2/3,ab/all

 2/3,AB/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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11802838   BIOSIS NO.: 199900048947
The indirect basal ganglia pathway exhibit parkinsonian-like changes
  in dopamine D2 receptors mutant mice.
AUTHOR: Dziewczapolski G(a); Murer M G(a); Rubinstein M; Salin P; Vila M;
  Ruberg M; Hirsch E; Kelly M A; Grandy D K; Low M J; Raisman-Vozari R;
  Gershanik O S(a)
AUTHOR ADDRESS: (a)ININFA, Buenos Aires**Argentina
JOURNAL: Society for Neuroscience Abstracts  24 (1-2):p593 1998
CONFERENCE/MEETING: 28th Annual Meeting of the Society for Neuroscience,
Part 1  Los Angeles, California, USA  November 7-12, 1998
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
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RECORD TYPE: Ci[redacted]ion
LANGUAGE: English

2/3,AB/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11732615 BIOSIS NO.: 199800514346
Novel synthesis and release of GABA in cerebellar granule cell cultures after infection with defective herpes simplex virus vectors expressing glutamic acid decarboxylase.
AUTHOR: New Kent C; Gale Karen; Martuza Robert L; Rabkin Samuel D(a)
AUTHOR ADDRESS: (a)Dep. Microbiol., Georgetown Univ. Medical Cent., 3970 Reservoir Road NW, Washington, DC 20007**USA
JOURNAL: Molecular Brain Research 61 (1-2):p121-135 Oct. 30, 1998
ISSN: 0169-328X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The inhibitory amino acid neurotransmitter gamma-aminobutyric acid (GABA) is synthesized from glutamate in a single step by the enzyme glutamatic acid decarboxylase (GAD). We sought to determine whether viral vectors containing GAD cDNA could be used to enhance synthesis and stimulation-evoked release of GABA in cultures of CNS neurons. For this purpose, we generated double-cassette defective herpes simplex virus (HSV) vectors that expressed one of the two GAD isoforms (GAD65 or GAD67), and Escherichia coli LacZ. Infection of cerebellar granule cell (CGC) cultures with vectors containing GAD cDNA resulted in a significant increase in isoform-specific expression of GAD, synthesis of GABA, and stimulation-evoked GABA release. GAD65 and GAD67 vector-infected neurons exhibited a comparable profile of GABA levels, synthesis and release, as well as GAD protein distribution. In CGCs cultured for 6 days in vitro (DIV), GABA synthesized after vector-derived GAD expression was released by treatment with glutamate or veratridine, but only in a Ca2+-independent fashion. In more mature (10 DIV) cultures, both Ca2+-dependent, K+ depolarization-induced, as well as Ca2+-independent, veratridine-induced, GABA release was significantly enhanced by GAD vector infection. Treatment of CGCs with kainic acid, which destroys most of the GABAergic neurons (< 1% remaining), did not prevent vector-derived expression of GAD nor synthesis of GABA. This suggests that defective HSV vector-derived GAD expression can be used to increase GABA synthesis and release in CNS tissue, even in the relative absence of GABAergic neurons. The use of such GAD vectors in the CNS has potential therapeutic value in neurologic disorders such as epilepsy, chronic pain, **Parkinson**'s and Huntington's disease.

2/3,AB/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11136825 BIOSIS NO.: 199799757970
Dopaminergic neurons intrinsic to the primate striatum.
AUTHOR: Betarbet Ranjita; Turner Robert; Chockkan Vijay; Delong Mahlon R; Allers Kelly A; Walters Judith; Levey Allan I; Greenamyre J Timothy(a)
AUTHOR ADDRESS: (a)Dep. Neurol., Emory Univ., 1639 Pierce Drive, WMB 6000, Atlanta, GA 30322**USA
JOURNAL: Journal of Neuroscience 17 (17):p6761-6768 1997
ISSN: 0270-6474
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Intrinsic, striatal tyrosine hydroxylase-immunoreactive (TH-i)

cells have received little consideration. In this study we have characterized these neurons and their regulatory response to nigrostriatal dopaminergic deafferentation. TH-i cells were observed in the striatum of both control and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys; TH-i cell counts, however, were 3.5-fold higher in the striatum of MPTP-lesioned monkeys. To establish the dopaminergic nature of the TH-i cells, sections were double-labeled with antibodies to dopamine transporter (DAT). Immunofluorescence studies demonstrated that nearly all TH-i cells were double-labeled with DAT, suggesting that they contain the machinery to be functional dopaminergic neurons. Two types of TH-i cells were identified in the striatum: small, aspiny, bipolar cells with varicose dendrites and larger spiny, multipolar cells. The aspiny cells, which were more prevalent, corresponded morphologically to the GABAergic interneurons of the striatum. Double-label immunofluorescence studies using antibodies to TH and glutamate decarboxylase (GAD-67), the synthetic enzyme for GABA, showed that 99% of the TH-i cells were GAD-67-positive. Very few (lt 1%) of the TH-i cells, however, were immunoreactive for the calcium-binding proteins calbindin and parvalbumin. In summary, these results demonstrate that the dopaminergic cell population of the striatum responds to dopamine denervation by increasing in number, apparently to compensate for loss of extrinsic dopaminergic innervation. Moreover, this population of cells corresponds largely with the intrinsic GABAergic cells of the striatum. This study also suggests that the adult primate striatum does retain some intrinsic capacity to compensate for dopaminergic cell loss.

2/3,AB/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10701179 BIOSIS NO.: 199799322324
Subthalamotomy in **parkinsonian** monkeys: Behavioural and biochemical analysis.
AUTHOR: Guridi J; Herrero M T; Luquin M R; Guillen J; Ruberg M; Laguna J; Vila M; Javoy-Agid F; Agid Y; Hirsch E; Obeso J A(a)
AUTHOR ADDRESS: (a)Neurol. Functional Neurosurg. Cent., Quiron Clin., Paseo Alcolea s/n, San Sebastian**Spain
JOURNAL: Brain 119 (5):p1717-1727 1996
ISSN: 0006-8950
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Nineteen Macaca fascicularis monkeys were divided into four different groups: Group A (n = 3), control; Group B (n = 3), monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP); Group C (n = 8), animals treated with MPTP in which the subthalamic nucleus (STN) was unilaterally lesioned by kainic acid injection; in Group D (n = 5), the STN was lesioned prior to MPTP administration. Subthalamotomy resulted in a bilateral improvement of tremor, spontaneous activity, bradykinesia (evaluated by a manual motor test) and freezing in Group C All these monkeys developed hemichorea contralateral to the lesion. The improvement was maintained and the hemichorea continued until death. The monkeys in group D showed severe hemiballism which persisted throughout MPTP administration and developed **parkinsonian** signs mainly on the side ipsilateral to the lesion. Analysis of the in situ hybridization of the mRNA coding for glutamic acid decarboxylase (GAD) ofMPTP monkeys showed a significant increase in the mean density of silver grains over every labelled neuron in the globus pallidum lateralis (56.8% over control) as well as the globus pallidus medialis (GPM) (45.7% over control) and the substantia nigra reticulata (SNR) (35.8% over control). No significant change was observed in the thalamic nucleus reticularis. Subthalamotomy (Groups C and D) produced a significant reduction in mRNA GAD expression on the side of the lesion in the GPM and the SNR (34% and

42.3%, respectively) with respect to the ipsilateral (non-lesioned) side and also when compared with **parkinsonian** monkeys. These results confirm and expand, at the cellular level, the paramount role of STN hyperactivity in the pathophysiology of **parkinsonism**. The therapeutic consequences of these findings for surgical treatment of **Parkinson**'s disease are discussed.

2/3,AB/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10517939 BIOSIS NO.: 199699139084
Consequence of nigrostriatal denervation and L-dopa therapy on the expression of glutamic acid decarboxylase messenger RNA in the pallidum.
AUTHOR: Herrero M-T(a); Levy R; Ruberg M; Luquin M R; Villares J; Guillen J ; Faucheux B; Javoy-Agid F; Guridi J; Agid Y; Obeso J A; Hirsch E C
AUTHOR ADDRESS: (a)Dep. Anatomy, Med. Sch., Univ. Murcia, 30071 Murcia** Spain
JOURNAL: Neurology 47 (1):p219-224 1996
ISSN: 0028-3878
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: To examine the consequences of nigrostriatal denervation and L-dopa treatment on the basal ganglia output system, we analyzed, by quantitative in situ hybridization, the messenger RNA coding for glutamic acid decarboxylase (M-r 67,000) (GAD-67 mRNA) in pallidal cells from patients with **Parkinson**'s disease (PD), monkeys rendered **parkinsonian** by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) receiving or not receiving L-dopa, and their respective control subjects. In MPTP-treated monkeys, the expression of GAD-67 mRNA was increased in cells from the internal pallidum, and this effect was abolished by L-dopa treatment. There were no differences in the levels of GAD-67 mRNA between patients with PD, who were all treated with L-dopa, and control subjects. These results indicate that the level of GAD-67 mRNA is increased in the cells of the internal pallidum after nigrostriatal dopaminergic denervation and that this increase can be reversed by L-dopa therapy.

2/3,AB/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10444218 BIOSIS NO.: 199699065363
Gamma-aminobutyric acid (GABA).
BOOK TITLE: Neuropeptides and neurotransmitters, 2nd edition
ORIGINAL LANGUAGE BOOK TITLE: Neuropeptides et neuromediateurs, 2e edition.
AUTHOR: Retaux S; Besson M-J
BOOK AUTHOR/EDITOR: Epelbaum J: Ed
AUTHOR ADDRESS: Inst. Neurosci. Neurochim. Neuroanat., Univ. Pierre Marie Curie, 75005 Paris**France
p45-52 1995
BOOK PUBLISHER: Editions Sandoz, Rueil-Malmaison, France
Editions INSERM (Institut National de la Sante et de la Recherche Medicale), 101, rue de Tolbiac, 75654 Paris Cedex 13, France
ISBN: 2-85598-659-1
DOCUMENT TYPE: Book
RECORD TYPE: Citation
LANGUAGE: French; Non-English

2/3,AB/7 (Item 7 from file: 5)

DIALOG(R)File Biosis Previews(R)

10001086 BIOSIS NO.: 199598456004
Activation of the subthalamic nucleus and pedunculopontine tegmentum: Does it affect dopamine levels in the substantia Nigra, nucleus accumbens and striatum?
AUTHOR: Jaffer A(a); Van Der Spuy G D(a); Russell V A; Mintz M; Taljaard J J F
AUTHOR ADDRESS: (a)Dep. Chem. Pathol., Univ. Stellenbosch, Tygerberg Hosp., PO Box 19113, Tygerberg 7505**South Africa
JOURNAL: Neurodegeneration 4 (2):p139-145 1995
ISSN: 1055-8330
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: **Parkinson**'s disease is a neurodegenerative disorder, of which the most prominent morphological feature is the progressive loss of dopaminergic nigrostriatal neurons. Increased glutamatergic transmission in the basal ganglia has been implicated in the pathophysiology of **Parkinson**'s disease (PD). This study investigated whether death of substantia nigra (SN) dopaminergic neurons could be caused by the hyperactivity of afferent pathways resulting in the release of a toxic dose of excitatory amino acids in the SN. Twice-daily unilateral stimulation of the subthalamic nucleus (STN) for 21 days, using two different pulse frequencies and current strengths, significantly increased amphetamine-induced rotation, whereas sham stimulated rats showed significantly reduced rotation. Striatal and SN dopamine (DA) levels were unaffected when compared to naive and sham stimulated rats. However, levels of the DA metabolite, homovanillic acid (HVA), were significantly higher in the ipsilateral anterior striata of rats that had been stimulated at high frequency (100 Hz) and low current (100 mu-A) as compared to sham treated animals. Stimulation of the pedunculopontine tegmentum (PPT), using a single kainic acid injection, did not affect DA concentration in the ipsilateral striatum and nucleus accumbens when compared to sham-treated rats. DA levels in the contralateral striatum and nucleus accumbens of lesioned rats were significantly higher than ipsilateral levels. DOPAC/DA ratios were lower in the contralateral striatum and nucleus accumbens, suggesting decreased DA turnover. Glutamic acid decarboxylase activity was significantly higher in the ipsilateral than the contralateral SN. The physical manifestations of PD require a large reduction in caudate and putamen DA levels and no such depletion was measured in this study. These results, therefore, do not support the hypothesis that **Parkinson**'s disease may result from an overstimulation of substantia nigral DA neurons by glutamate afferents originating from the STN or PPT.

2/3,AB/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09925166 BIOSIS NO.: 199598380084
Effects of Nigrostriatal denervation and L-Dopa Therapy on the GABAergic Neurons of the Striatum in MPTP-treated Monkeys and **Parkinson**'s Disease: An In Situ Hybridization Study of GAD-67 mRNA.
AUTHOR: Levy R; Herrero M T; Ruberg M; Villares J; Faucheux B; Guridi J; Guillen J; Luquin M R; Javoy-Agid F; Obeso J A; Agid Y; Hirsch E C(a)
AUTHOR ADDRESS: (a)INSERM U.289, Hopital Salpetriere, 47 boulevard l'Hopital, 75651 Paris Cedex 13**France
JOURNAL: European Journal of Neuroscience 7 (6):p1199-1209 1995
ISSN: 0953-816X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract

LANGUAGE: Engli

ABSTRACT: The effects of nigrostriatal denervation and L-dopa therapy on GABAergic neurons were analysed in patients with **Parkinson**'s disease and in monkeys rendered **parkinsonian** by MPTP intoxication. The expression of the messenger RNA coding for the 67 kDa isoform of glutamic acid decarboxylase (GAD-67 mRNA), studied by quantitative in situ hybridization, was used as an index of the GABAergic activity of the striatal neurons. A significant increase in GAD-67 mRNA expression, generalized to all GABAergic neurons, was observed in MPTP-treated monkeys compared to control monkeys in the putamen and caudate nucleus (+44 and +67% respectively), but not in the ventral striatum. L-Dopa therapy significantly reduced GAD-67 mRNA expression in the putamen and caudate nucleus to levels similar to those found in control monkeys. However, the return to normal of GAD-67 mRNA expression was not homogeneous across all neurons since it was followed by an increase of labelling in one subpopulation of GABAergic neurons and a decrease in another. These data suggest that in MPTP-treated monkeys the degeneration of nigrostriatal dopaminergic neurons results in a generalized increase in GABAergic activity in all the GABAergic neurons of the striatum, which is partially reversed by L-dopa therapy. As the expression of GAD-67 mRNA is less intense in the ventral than in the dorsal striatum, this increase in striatal GABAergic activity may be related to the severity of nigrostriatal denervation. In **parkinsonian** patients who had been chronically treated with L-dopa, GAD-67 mRNA expression was significantly decreased in all GABAergic neurons, in the caudate nucleus (by 44%), putamen (by 43.5%) and ventral striatum (by 26%). The opposite variation of GAD-67 mRNA in patients with **Parkinson**'s disease, compared with MPTP-treated monkeys, might be explained by the combination of chronic nigrostriatal denervation and long-term L-dopa therapy.

2/3,AB/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09428760 BIOSIS NO.: 199497437130
Effect of chronic L-dopa treatment of gene expression of preproenkephalin, preprotachykinin and glutamic acid decarboxylase in the striatum of 6-hydroxydopamine lesioned rats.
AUTHOR: Zeng B-Y; Jenner P; Marsden C D
AUTHOR ADDRESS: Neurodegenerative Disease Res. Cent., Pharmacol. Group, Biomed. Sci. Div., King's Coll., Manresa Rd.**UK
JOURNAL: British Journal of Pharmacology 112 (PROC. SUPPL.):p618P 1994
CONFERENCE/MEETING: Meeting of the British Pharmacological Society Manchester, England, UK April 13-15, 1994
ISSN: 0007-1188
RECORD TYPE: Citation
LANGUAGE: English

2/3,AB/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09040536 BIOSIS NO.: 199497048906
Dopaminergic regulation of glutamic acid decarboxylase mRNA expression and GABA release in the striatum: A review.
AUTHOR: Lindefors Nils
AUTHOR ADDRESS: Dep. Pharmacol., Karolinska Inst., P.O. Box 60 400, S-104 01 Stockholm**Sweden
JOURNAL: Progress in Neuro-Psychopharmacology & Biological Psychiatry 17 (6):p887-903 1993
ISSN: 0278-5846
DOCUMENT TYPE: Literature Review

RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: 1. The majority of neurons in the striatum (caudate-putamen, dorsal striatum; nucleus accumbens, ventral striatum) and in striatal projection regions (the pallidum, the entopeduncular nucleus and substantia nigra reticulata) use gamma-aminobutyric acid (GABA) as transmitter and express glutamic acid decarboxylase (GAD; rate limiting enzyme) in the synthesis of GABA. GABA is the major inhibitory transmitter in the mammalian brain. 2. GAD in brain is present as two isoenzymes, GAD-65 and GAD-67. GAD-65 is largely present as an inactive apoenzyme, which can be induced by nerve activity, while most GAD-67 is present as a pyridoxal phosphate-bound permanently active holoenzyme. Thus GAD-65 and GAD-67 seem to provide a dual system for the control of neuronal GABA synthesis. 3. GAD mRNA expression can be visualized and quantified using in situ hybridization, and GABA release can be quantified using in vivo microdialysis. 4. Different populations of GABA neurons can be distinguished in both dorsal and ventral striatum as well as in other parts of the basal ganglia. 5. Inhibition of dopaminergic transmission in the striatum by lesion of dopamine neurons or by neuroleptic treatment is followed by an increased release of GABA and increased expression of GAD67 mRNA in a subpopulation of striatal medium-sized neurons which project to the globus pallidus, and increased striatal GAD enzyme activity. 6. Increased dopaminergic transmission by repeated but not single doses of amphetamine is followed by decreased striatal GABA release and decreased GAD-67 mRNA expression in a subpopulation of medium-sized neurons in the striatum. 7. Two populations of medium-sized GABA neurons in the striatum seem to be under tonic dopaminergic influence. The majority of these GABA neurons are under inhibitory influence, whereas a small number seem to be stimulated by dopamine. 8. Specific changes in activity in subpopulations of striatal GABA neurons probably mediate the dopamine-dependent hypokinetic syndrome seen in **Parkinson**'s disease and following neuroleptic treatment.

2/3,AB/11 (Item 11 from file: 5)

09008089 BIOSIS NO.: 199497016459
Decreased GAD mRNA expression in internal pallidum and substantia nigra pars reticulata neurons after subthalamotomy in MPTP treated monkeys.
AUTHOR: Guridi J(a); Herrero M-T(a); Ruberg M(a); Hirsch E C; Guillen J(a); Luquin M R(a); Javoy-Agid F; Agid Y; Obeso J A(a)
AUTHOR ADDRESS: (a)Neurol. Exper. Univ. Navarra, 31080 Pamplona**Spain
JOURNAL: Society for Neuroscience Abstracts 19 (1-3):p133 1993
CONFERENCE/MEETING: 23rd Annual Meeting of the Society for Neuroscience Washington, D.C., USA November 7-12, 1993
ISSN: 0190-5295
RECORD TYPE: Citation
LANGUAGE: English

2/3,AB/12 (Item 12 from file: 5)

09008088 BIOSIS NO.: 199497016458
Changes in GAD mRNA expression in neurons of the internal pallidum in **parkinsonian** monkeys after L-dopa therapy.
AUTHOR: Herrero M-T(a); Ruberg M(a); Hirsch E C(a); Guridi J; Luquin M R; Guillen J; Javoy-Agid F(a); Agid Y(a); Obeso J A
AUTHOR ADDRESS: (a)INSERM U289, Hopital Salpetriere, 75651 Paris**France
JOURNAL: Society for Neuroscience Abstracts 19 (1-3):p132 1993
CONFERENCE/MEETING: 23rd Annual Meeting of the Society for Neuroscience

Washington, D.C., USA November 7-12, 1993
ISSN: 0190-529
RECORD TYPE: Citation
LANGUAGE: English

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(antisens? or ribozym? or triplex)
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            1172  GAD65
             725  GAD67
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           36173  ANTISENS?
            6567  RIBOZYM?
            2973  TRIPLEX
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 5/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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10558782 20422530

Neonatal 6-hydroxydopamine **treatment** affects **GABA**(A) receptor subunit expression in the frontal cortex but not the hippocampus of rats during postnatal development.

Podkletnova I; Makela R; Korpi ER; Luddens H; Helen P; Alho H

International Graduate School of Neuroscience, Medical School, University of Tampere, Tampere, Finland.

Developmental neuroscience (SWITZERLAND) 2000, 22 (4) p296-302, ISSN 0378-5866 Journal Code: EC5

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The influence of neonatal administration of 6-hydroxydopamine (6-OHDA) on the maturation of **GABA** (A) receptors in the frontal cortex and hippocampus was studied using 5- to 40-day-old rats. In situ hybridization with **antisense** oligonucleotide probes was performed for alpha(1), alpha(2), alpha(5), beta(2), beta(3) and gamma(2) subunit mRNAs of the **GABA**(A) receptor. We demonstrated that neonatal **treatment** with 6-OHDA temporarily delays the postnatal transcription of the alpha(1) and gamma(2) subunits in the rat prefrontal cortex, as assessed by in situ hybridization histochemistry. The effect was selective for these subunits (the alpha(2), alpha(5), beta(2), and beta(3) subunit mRNAs remained unchanged) and for this region (the mRNA levels in the hippocampus were not changed). The reduction in mRNA levels at early postnatal stages (postnatal day 5, PD5, and PD10) also affected the subunit protein levels, as shown by immunohistochemistry for the alpha(1) subunit, and the formation of **GABA** (A) receptor-associated picrotoxinin-insensitive TBPS binding sites, as shown by autoradiography. Our findings indicate that without a noradrenergic influence, the maturation of GABAergic interneurons in the frontal cortex is transiently delayed (from PD5 to PD40). However, it is possible that this transient reduction of the expression of certain **GABA** subunits - caused by depletion of noradrenergic innervation - cannot cause a lasting alteration to the GABAergic function in the prefrontal cortex.

5/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10546965 20344441
Neonatal 6-hydroxydopamine **treatment** affects **GABA**(A) receptor subunit expression during postnatal development of the rat cerebellum.
Podkletnova I; Alho H; Makela R; Luddens H; Helen P; Korpi ER
International Graduate School of Neuroscience, Medical School, University of Tampere, PO Box 607, 33101, Tampere, Finland.
International journal of developmental neuroscience (ENGLAND) Oct 2000, 18 (6) p565-72, ISSN 0736-5748 Journal Code: 126
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Neurotoxic elimination of noradrenergic terminals by 6-hydroxydopamine (6-OHDA) leads to alteration of the granule cell layer formation. We have studied the developmental expression of **GABA**(A) receptor subunits in rat cerebellum after neonatal administration of 6-OHDA during the first postnatal month of life. 6-OHDA was injected subcutaneously. The expression of **GABA**(A) receptor subunits was studied by in situ hybridization and immunohistochemistry. The alterations were observed in the neocerebellum - the part of the cerebellum which starts development postnatally. The migration of granule cells was delayed, and the total area of the granule cell layer in the neocerebellum from 6-OHDA-**treated** rats was reduced to 22.6+/-5% of the corresponding area from control rats. In situ hybridization with subunit-specific **antisense** oligonucleotide probes was performed for alpha1, alpha2, alpha3, alpha5, alpha6, beta1, beta2, gamma1 and gamma2 subunits of the **GABA**(A) receptor. In neocerebellum, 6-OHDA **treatment** caused a significant reduction in the alpha1, alpha6 and gamma2 subunit mRNA levels. The expression of the other subunits was not changed. It has been shown that in the postnatal cerebellum alpha1 and alpha6 subunits can be detected in granule cells only when the cells had migrated to their final destination. Our findings indicate that a noradrenergic influence may be necessary for the normal maturation and migration of cerebellar granule cells.

5/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10507440 20325016
Antidepressant effects on **GABA**-stimulated 36Cl(-) influx in rat cerebral cortex are altered after **treatment** with **GABA**(A) receptor **antisense** oligodeoxynucleotides.
Malatynska E; Crites GJ; Harrawood D; Goldenberg R; Matheson GK
Indiana University School of Medicine, Department of Pharmacology and Toxicology, 8600 University Boulevard, Evansville, IN 47712, USA. emalatyn@iupui.edu
Brain research (NETHERLANDS) Jun 30 2000, 869 (1-2) p78-84, ISSN 0006-8993 Journal Code: B5L
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Antidepressants act at the **GABA**(A) receptor to inhibit **GABA** -stimulated 36Cl(-) influx and **GABA** reduction of [35S]TBPS binding. This study examined how selective knock-down (via **antisense** oligodeoxynucleotides, aODNs) of **GABA**(A) receptor subunits modified antidepressant activity. The specific aODNs used were for the alpha1, beta1, beta2 or gamma2 subunits of the **GABA**(A) receptor. The aODN microinjections reduced corresponding **GABA**(A) receptor subunit mRNA levels by 30-40% as assessed by RT-PCR. The inhibitory effect of the antidepressants amitriptyline and mianserin on **GABA** -stimulated 36Cl(-) influx was decreased after microinjections of alpha1, beta1, or beta2 subunit aODNs but potentiated after microinjections of gamma2 subunit

aODNs. This pattern of aODNs effect on amitriptyline and mianserin modulation of **GABA** -stimulated 36Cl(-) influx was the same for both antidepressants and similar to **GABA** but different than that of diazepam and bicuculline. We conclude that multiple subunits of the **GABA** (A) receptor regulate the effect of amitriptyline and mianserin on the **GABA** (A) receptor chloride ionophore complex. However, the exact identity of the subunit mediating the direct or allosteric modulation of the antidepressant effect on **GABA** -stimulated 36Cl(-) influx remains unclear.

5/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10460083 20306725
GABA-transaminase **antisense** oligodeoxynucleotide modulates cocaine- and pentylenetetrazol-induced seizures in mice.
Abel MS; Kohli N
Department of Cell Biology and Anatomy FUHS/The Chicago Medical School, North Chicago, IL 60064, USA. abelm@finchcms.edu
Metabolic brain disease (UNITED STATES) Dec 1999, 14 (4) p253-63, ISSN 0885-7490 Journal Code: M9L
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The mechanism of action of many anticonvulsive agents is to increase the function of the GABAergic system. Inhibition of **GABA**-Transaminase (**GABA**-T), the degradative enzyme for **GABA**, increases **GABA** levels in the brain. In this study, **antisense** oligodeoxynucleotides (ASO) targeted at the start codon region of **GABA**-Transaminase mRNA were used to modify seizure activity. Mice were **treated** , by intracerebroventricular injection, with **antisense** oligos or appropriate controls. At various times after **treatment**, the animals were challenged with cocaine (70 mg/kg, i.p.) and observed for seizure activity. At 15 hours after **treatment**, 1.152 and 1.44 nmol **antisense** oligo blocked cocaine-induced seizures. There was no effect of **antisense** oligo 8 or 36 hours after **treatment**. In addition, **treatment** with 7.2 nmol **antisense** oligo prevented pentylenetetrazol-induced seizures. These data demonstrate the modulation of seizure threshold using **antisense** oligodeoxynucleotides to **GABA**-T.

5/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10380162 20223562
The amygdala: site of genomic and nongenomic arousal of aldosterone-induced sodium intake.
Sakai RR; McEwen BS; Fluharty SJ; Ma LY
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Kidney international (UNITED STATES) Apr 2000, 57 (4) p1337-45, ISSN 0085-2538 Journal Code: KVB
Contract/Grant No.: DK48061, DK, NIDDK; MH43787, MH, NIMH
Languages: ENGLISH
Document type: JOURNAL ARTICLE
BACKGROUND.: Mineralocorticoids act on the brain to influence sodium intake, and they do so via intracellular type I receptors and possibly also via a direct membrane action, as they do in the kidney. One brain area implicated by lesion studies investigating the regulation of sodium appetite aroused by adrenal steroids is the amygdala. METHODS: To examine the mechanism by which mineralocorticoids act in the amygdala to arouse salt intake via a genomic and or membrane mode of action, rats were

bilaterally fit with cannulae directed to terminate in the amygdala. The genomic action of mineralocorticoids in arousing sodium intake was investigated by the administration of **antisense** oligodeoxynucleotides (ASDNs) against the mineralocorticoid receptor, and its effects on deoxycorticosterone (DOCA)-induced sodium intake over the course of several days was examined. The nongenomic action of mineralocorticoids on sodium intake was investigated by implantation into the amygdala of DOCA, aldosterone (ALDO), or their A-ring-reduced tetrahydro derivatives, 15 minutes prior to access to saline. Sodium intake was monitored immediately thereafter. RESULTS: **Treatment** of rats in the amygdala with ASDN against the mineralocorticoid receptor inhibited DOCA-induced sodium intake, whereas ASDN against the glucocorticoid receptor or sense/scrambled sequences had no effect. DOCA and ALDO increased saline intake within 15 minutes after steroid application. Similarly, the application of A-ring-reduced 3beta,5beta tetrahydroaldosterone and 5 alpha-tetrahydrodeox ycorticosterone produced the same increases in sodium intake. CONCLUSIONS: Together, the data imply that adrenal steroids, in addition to acting through classic cytosolic receptors, may also act on membrane receptor systems, producing rapid changes in behavior.

5/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10361859 20044821
Abnormal synapse formation in agrin-depleted hippocampal neurons.
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Journal of cell science (ENGLAND) Dec 1999, 112 (Pt 24) p4729-38, ISSN 0021-9533 Journal Code: HNK
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Agrin, a 200 kDa extracellular matrix protein, participates in the maturation of the postsynaptic target at the neuromuscular junction. Although agrin has also been detected in central neurons, little is known about its role in the formation of their synapses. In the present study, the pattern of expression, localization and function of agrin in developing hippocampal neurons were analyzed. The results indicate that an increase in agrin protein levels precedes synaptogenesis in cultured hippocampal neurons. This increase in agrin expression is accompanied by its extracellular deposition along the distal third of the axon. To investigate whether agrin plays a role during synapse formation, its expression in cultured hippocampal neurons was suppressed by means of **antisense** oligonucleotide **treatment** . The suppression of agrin expression results in the impairment of dendritic development and the formation of fewer synapses than in non-**treated** or sense-**treated** neurons. Moreover, this decreased synaptic density is accompanied by a selective inhibition of the clustering of **GABA** receptors. These results lead to the conclusion that agrin may be an important regulator of the maturation of dendrites and synaptogenesis in central neurons.

5/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10300560 20031234
Effects of **treatment** with **GABA**(A) receptor subunit **antisense** oligodeoxynucleotides on **GABA**-stimulated 36Cl- influx in the rat cerebral cortex.
Malatynska E; Matheson GK; Goldenberg R; Crites GJ; Schindler NL; Weinzapfel D; Harrawood D; Yochum A; Tunnicliff G
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Medicine, Evans[redacted]le 47712, USA. emalatyn@iupui.[redacted]
Neurochemistry international (ENGLAND) Jan 2000, 36 (1) p45-54, ISSN 0197-0186 Journal Code: BNU
Languages: ENGLISH
Document type: JOURNAL ARTICLE

GABA(A) receptor function was studied in cerebral cortical vesicles prepared from rats after intracerebroventricular microinjections of **antisense** oligodeoxynucleotides (aODNs) for alpha1, gamma2, beta1, beta2 subunits. **GABA** (A) receptor alpha1 subunit aODNs decreased alpha1 subunit mRNA by 59+/-10%. Specific [3H]**GABA** binding was decreased by alpha1 or beta2 subunit aODNs (to 63+/-3% and 64+/-9%, respectively) but not changed by gamma2 subunit aODNs (94+/-5%). Specific [3H]flunitrazepam binding was increased by alpha1 or beta2 subunit aODNs (122+/-8% and 126+/-11%, respectively) and decreased by gamma2 subunit aODNs (50+/-13%). The "knockdown" of specific subunits of the **GABA**(A)receptor significantly influenced **GABA** -stimulated 36Cl- influx. Injection of alpha1 subunit aODNs decreased basal 36Cl- influx and the **GABA** Emax; enhanced **GABA** modulation by diazepam; and decreased antagonism of **GABA** activity by bicuculline. Injection of gamma2 subunit aODNs increased the **GABA** Emax; reversed the modulatory efficacy of diazepam from enhancement to inhibition of **GABA** -stimulation; and reduced the antagonist effect of bicuculline. Injection of beta2 subunit aODNs reduced the effect of diazepam whereas **treatment** with beta1 subunit aODNs had no effect on the drugs studied. Conclusions from our studies are: (1) alpha1 subunits promote, beta2 subunits maintain, and gamma2 subunits suppress **GABA** stimulation of 36Cl- influx; (2) alpha1 subunits suppress, whereas beta2, and gamma2 subunits promote allosteric modulation by benzodiazepines; (3) diazepam can act as an agonist or inverse agonist depending on the relative composition of the receptor subunits: and (4) the mixed competitive/non-competitive effects of bicuculline result from activity at alpha1 and gamma2 subunits and the lack of activity at beta1 and beta2 subunits.

5/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10148187 99437435
The effects of calbindin D-28K and parvalbumin **antisense** oligonucleotides on the survival of cultured Purkinje cells.
Vig PJ; McDaniel DO; Subramony SH; Qin Z
Department of Neurology, University of Mississippi Medical Center, Jackson 39216, USA. pvig@neurology.umsmed.edu
Research communications in molecular pathology and pharmacology (UNITED STATES) Mar 1999, 103 (3) p249-59, ISSN 1078-0297 Journal Code: B2X
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The role of calcium binding proteins, calbindin D-28k (CaB) and parvalbumin (PV) in Purkinje cell survival was investigated using oligonucleotide **antisense** strategy. Purkinje cell enriched cultures were prepared from the cerebella of 0-1 day old Balb/c mouse pups. Purkinje cells were identified by size, asymmetric arbors, immunoreactivity to CaB and PV, uptake of gamma-aminobutyric acid (**GABA**) and failure to express glial fibrillary acidic protein. The cells at different days in vitro were **treated** with **antisense** or mismatched **antisense** phosphorothioate oligonucleotides for CaB and PV mRNA (complexed with lipofectin). Neuronal specific [3H]-**GABA** uptake was used as a measure of Purkinje cell survival. The cultures **treated** for 24 h with **antisense** oligos (CaB+PV) showed a significant decrease in [3H]-**GABA** uptake as compared with the cultures **treated** with lipofectin alone or with lipofectin + mismatched **antisense** oligos to CaB and PV mRNA. The results of the present study suggest that the expression of calcium buffering proteins CaB and PV may have a significant

involvement in [redacted]kinje cell viability.

5/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09846919 99175185
alpha-soluble N-ethylmaleimide-sensitive factor attachment protein is expressed in pancreatic beta cells and functions in insulin but not gamma-aminobutyric acid secretion.
Nagamatsu S; Watanabe T; Nakamichi Y; Yamamura C; Tsuzuki K; Matsushima S
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Journal of biological chemistry (UNITED STATES) Mar 19 1999, 274 (12) p8053-60, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The function of soluble N-ethylmaleimide-sensitive attachment protein-alpha (alpha-SNAP) in exocytosis still remains obscure. This study was conducted to determine the physiological role of alpha-SNAP in the secretion of insulin and gamma-aminobutryric acid (**GABA**) from pancreatic beta cells. Reverse transcriptase-polymerase chain reaction analysis of total RNA isolated from rat islets disclosed alpha-SNAP, but not beta-SNAP, mRNA expression, and an immunofluorescence study of rat pancreas showed that alpha-SNAP was present predominantly in the cytoplasm of the islets of Langerhans. alpha-SNAP overexpression in rat islets enhanced insulin release relative to the control levels. An in vitro binding study showed that both wild-type alpha-SNAP and C-terminal-deleted alpha-SNAP mutant (1-285) can bind to syntaxin 1A. alpha-SNAP mutant (1-285) was overexpressed to evaluate its activity as dominant-negative effector on insulin release. Overexpression of alpha-SNAP mutant (1-285) in rat islets and MIN6 cells decreased glucose-stimulated insulin release to about 50% of the control levels. Suppression of endogeneous alpha-SNAP in MIN6 cells by **treatment** with an **antisense** phosphorothioate oligonucleotide resulted in inhibition of insulin release. In order to examine if alpha-SNAP functions in exocytosis from synaptic-like microvesicles in pancreatic beta cells, the functional role of alpha-SNAP in **GABA** release from MIN6 cells was studied. The data showed no effect of alpha-SNAP mutant (1-285) overexpression on **GABA** release. We conclude that 1) alpha-SNAP plays a crucial role in insulin exocytosis via large dense core vesicles, but not **GABA** released via synaptic-like microvesicles, in pancreatic beta cells; and 2) the interaction of alpha-SNAP and syntaxin 1A may play an important role in the insulin exocytotic process.

5/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09823500 99079264
Functional neuroanatomy of the basal ganglia as studied by dual-probe microdialysis.
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Nuclear medicine and biology (ENGLAND) Nov 1998, 25 (8) p743-6, ISSN 0969-8051 Journal Code: BOO
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Dual probe microdialysis was employed in intact rat brain to investigate the effect of intrastriatal perfusion with selective dopamine D1 and D2 receptor agonists and with c-fos **antisense** oligonucleotide on (a) local **GABA** release in the striatum; (b) the internal segment of the

globus pallidus and the substantia nigra pars reticulata, which is the output site of the strionigral **GABA** pathway; and (c) the external segment of the globus pallidus, which is the output site of the striopallidal **GABA** pathway. The data provide functional in vivo evidence for a selective dopamine D1 receptor-mediated activation of the direct strionigral **GABA** pathway and a selective dopamine D2 receptor inhibition of the indirect striopallidal **GABA** pathway and provides a neuronal substrate for parallel processing in the basal ganglia regulation of motor function. Taken together, these findings offer new therapeutic strategies for the **treatment** of dopamine-linked disorders such as Parkinson's disease, Huntington's disease, and schizophrenia.

5/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09818722 99072690

Antisense oligonucleotide to **GABA**(A) receptor gamma2 subunit induces limbic status epilepticus.

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Journal of neuroscience research (UNITED STATES) Dec 15 1998, 54 (6) p863-9, ISSN 0360-4012 Journal Code: KAC
Contract/Grant No.: NS28772, NS, NINDS
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Gamma-Aminobutyric acid (**GABA**) is the principal inhibitory neurotransmitter in the brain. A deficiency of GABAergic inhibition mediated via the GABAA receptor complex has for a long time been suspected to be a central factor in epileptogenesis. Status epilepticus is a condition of sustained and prolonged excitation of neuronal circuits, as detected by epileptiform discharges in the electroencephalogram (EEG). Reduction of GABAA receptor-mediated hippocampal inhibition has been implicated in the development of status epilepticus. The present study provides direct evidence of a link between the GABAA receptor and epilepsy. We show that selective inhibition of the expression of the GABAA receptor gamma2 subunit in the rat hippocampus by means of **antisense** oligonucleotides leads to spontaneous electrographic seizures that evolve into profound limbic status epilepticus, ultimately resulting in severe neurodegenerative changes. Concurrent **treatment** with diazepam prevents the development of status epilepticus and markedly reduces neuronal cell loss. These findings strongly support the hypothesis that the GABAA receptor is critically involved in the pathogenesis of seizures and status epilepticus.

5/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09792276 99124487

A role of gamma-amino butyric acid (**GABA**) and glutamate in control of puberty in female rhesus monkeys: effect of an **antisense** oligodeoxynucleotide for **GAD67** messenger ribonucleic acid and MK801 on luteinizing hormone-releasing hormone release.

Kasuya E; Nyberg CL; Mogi K; Terasawa E
Wisconsin Regional Primate Research Center, University of Wisconsin-Madison, 53715-1299, USA.

Endocrinology (UNITED STATES) Feb 1999, 140 (2) p705-12, ISSN 0013-7227 Journal Code: EGZ
Contract/Grant No.: HD-11355, HD, NICHD; HD-15433, HD, NICHD; RR-00167, RR, NCRR
Languages: ENGLISH

Document type: JOURNAL ARTICLE

Previously we have shown that gamma-aminobutyric acid (**GABA**) is an inhibitory neurotransmitter restricting the pubertal increase in LHRH release in juvenile monkeys, and that interfering with **GABA** synthesis with an **antisense** oligodeoxynucleotide (AS) for glutamic acid decarboxylase (**GAD67**) mRNA results in an increase in LHRH release in prepubertal monkeys. **GAD67** is a catalytic enzyme that synthesizes **GABA** from glutamate. To further clarify the role of **GABA** in puberty, we examined whether the inhibition of LHRH release by **GABA** continues after the onset of puberty and whether input from glutamatergic neurons plays any role in the onset of puberty when **GABA** inhibition declines, using a push-pull perfusion method. In Study I, the effects of the AS **GAD67** mRNA on LHRH release in pubertal monkeys (34.3 +/- 1.5 months of age, n = 8) were examined, and the results were compared with those in prepubertal monkeys (18.5 +/- 0.4 months, n = 12). Direct infusion of AS **GAD67** (1 microM) into the stalk-median eminence (S-ME) for 5 h stimulated LHRH release in both prepubertal and pubertal monkeys. However, the increase in LHRH release in pubertal monkeys was significantly ($P < 0.01$) smaller than that in prepubertal monkeys. Infusion of a scrambled oligo as a control was without effect in either group. In Study II, to examine the possibility that an increase in glutamate tone after the reduction of an inhibitory **GABA** tone contributes to the AS **GAD67**-induced LHRH increase, the effects of the NMDA receptor blocker MK801 (5 microM) on LHRH release were tested in monkeys **treated** with AS **GAD67**. MK801 infusion into the S-ME during the **treatment** of AS **GAD67** (1 microM) suppressed the AS **GAD67**-induced LHRH release in both age groups. MK801 alone did not cause any significant effect in either group. The data are interpreted to mean that **GABA** continues to suppress LHRH release after the onset of puberty, although the degree of suppression is weakened considerably after the onset of puberty, and that the increased LHRH release after AS **GAD67 treatment** may be partly due to an increase in glutamate tone mediated by NMDA receptors, as well as due to the decrease in **GABA** release following the decrease in **GAD** synthesis. Taken together, the present results suggest that **GAD** may play an important role in the onset and progress of puberty in nonhuman primates.

5/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09790285 99057756

Intra-accumbens infusions of **antisense** oligodeoxynucleotides to one isoform of glutamic acid decarboxylase mRNA, **GAD65**, but not to **GAD67** mRNA, impairs sustained attention performance in the rat.

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Brain research. Cognitive brain research (NETHERLANDS) Jan 1999, 7 (3) p269-83, ISSN 0926-6410 Journal Code: BLW

Contract/Grant No.: NS32938, NS, NINDS; MH01072, MH, NIMH; T32 MH19936, MH, NIMH

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The effects of bilateral infusions of **antisense** oligodeoxynucleotides (ODNs) for the two isoforms of glutamic acid decarboxylase (**GAD65**; **GAD67**) into the nucleus accumbens on the performance of intact rats in a task designed to assess sustained attention were tested. The task required the animals to discriminate between signal and non-signal events. Signals and non-signals were presented randomly and unpredictably. The task generated all four response types of a sustained attention task, i.e., hits, misses, correct rejections, false alarms. Infusions of the scrambled sequence ODNs did not affect performance. Likewise, infusions of the **GAD67** ODNs failed to produce any effect.

However, infusions of the **GAD65** ODNs into the nucleus accumbens resulted in a robust and reliable decrease in the relative number of hits. Similarly, the combined infusion of **GAD65**+67 ODNs impaired the hit rate but did not affect the animals' ability to reject non-signals. Following each **treatment** series, performance rapidly returned to baseline, further indicating the specificity and reversibility of the effects of the infusions of the ODNs. While these data suggest that translation arrest of specifically the **GAD65** isoform of the enzyme in the nucleus accumbens impairs attentional performance, the neuronal mechanisms mediating these effects remain unsettled. Copyright 1999 Elsevier Science B.V.

5/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09716825 99026202

Decreased benzodiazepine binding with little effect on gamma-aminobutyric acid binding in rat brain after **treatment** with **antisense** oligodeoxynucleotide to the gamma-aminobutyric acidA receptor gamma-2 subunit.

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Journal of pharmacology and experimental therapeutics (UNITED STATES) Nov 1998, 287 (2) p752-9, ISSN 0022-3565 Journal Code: JP3

Contract/Grant No.: DA02194, DA, NIDA

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Benzodiazepine potentiation of gamma-aminobutyric acid (**GABA**) neurotransmission is associated with the presence of a gamma-2 subunit in the GABAA receptor. A method was developed to modify the gamma-2 subunit expression in adult rat brain. Unilateral intracerebroventricular (i.c.v.) infusion of a 17-base phosphorothioate-modified **antisense** oligodeoxynucleotide (ASO) was performed every 12 hr for 3 days. Controls were **treated** with a sense oligodeoxynucleotide. Parasagittal brain sections were used for quantitative autoradiographic analysis of radioligand binding. ASO **treatment** caused a 15% to 25% decrease of specific [3H]flunitrazepam binding in most brain areas, with statistically significant decreases in frontal cortex, cerebellar molecular layer, zona reticulata of substantia nigra and CA3 of hippocampus. In contrast, [3H]muscimol binding was not changed. [3H]**GABA** binding was also unchanged, except for a 10% decrease in cerebellar granule cell layer. The effect on the chloride channel of the GABAA receptor complex was examined by 4'-ethynyl-4-n-[2, 3-3H2]propylbicycloorthobenzoate binding; most brain areas showed small decreases in 4'-ethynyl-4-n-[2, 3-3H2]propylbicycloortho benzoate binding. However, hippocampal regions showed much larger decreases. Binding of the adenosine A1 receptor antagonist [3H]8-cyclopentyl-1,3-dipropylxanthine was used to examine possible secondary effects of the ASO. There was a decrease in [3H]8-cyclopentyl-1,3-dipropylxanthine binding, but this was much smaller than the change in [3H]flunitrazepam binding, and no area showed a significant effect. Quantitative immunoblotting with a monoclonal antibody that recognizes GABAA receptor beta-2 and beta-3 subunits showed no change in immunoreactivity in cerebellar tissue after ASO **treatment**. The results indicate a selective effect on benzodiazepine binding to GABAA receptors and a possible change in receptor subunit composition.

5/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09655254 98075846

Antisense inhibition of R-cognin expression modulates differentiatio retinal neurons in vitro.

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Department of Biology, Boston University, Boston, MA 02215, USA.

Molecular vision (UNITED STATES) Nov 21 1997, 3 p12, ISSN 1090-0535 Journal Code: CWP
Languages: ENGLISH
Document type: JOURNAL ARTICLE

PURPOSE: Retina cognin (R-cognin) is a 50 kDa membrane-associated polypeptide expressed during retinogenesis where it is involved in mediating tissue-specific cell-cell interactions. In addition to its intercellular role in aggregation, R-cognin may act as a cell surface signaling molecule. An **antisense** oligonucleotide was used to inhibit R-cognin expression and to investigate the effects of this inhibition on subsequent neuronal differentiation. METHODS: Cultures of retina cells were prepared from 6 day (E6) and 8 day (E8) chicken embryos and were incubated with a deoxyoligonucleotide complimentary to 20 bases of the sequence encoding R-cognin or random oligonucleotides. The levels of choline acetyltransferase (ChAT) and glutamic acid decarboxylase (**GAD**), markers of cholinergic and GABAergic differentiation, respectively, were detected by Western blots on protein extracts from **treated** cultures. RESULTS: The **antisense treatment** inhibited ChAT levels at E6 and **GAD** levels at E8. The **treatment** resulted in no decrease in the level of the enzyme glyceraldehyde 3-phosphate dehydrogenase. A random oligonucleotide did not affect the levels of any of the proteins. CONCLUSIONS: These results confirm the cell recognition role of R-cognin and suggest that it is important in intracellular signaling cascades necessary for normal retina development.

5/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09642776 98340029

Antisense inhibition of striatal GABAA receptor proteins decreases **GABA** -stimulated chloride uptake and increases cocaine sensitivity in rats.

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Brain research. Molecular brain research (NETHERLANDS) Jun 15 1998, 57 (2) p310-20, ISSN 0169-328X Journal Code: MBR
Contract/Grant No.: AA 09115, AA, NIAAA; AA 07561, AA, NIAAA
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The functional status of striatal GABAA receptors appears to be inversely related to the magnitude of cocaine-induced behaviors. Exposure of striatum to **antisense** oligodeoxynucleotides (ASODNs) targeted to the mRNAs for the alpha 2 and the beta 3 subunits of the GABAA receptor should decrease expression of receptor proteins and therefore might be expected to increase cocaine sensitivity. ASODNs, scrambled ODNs or saline were injected into right lateral ventricle of rats and behavioral responses to cocaine were tested 18-20 h after **treatment** . Animals injected separately with alpha 2 or beta 3 ASODNs exhibited increased behavioral sensitivity to cocaine compared to rats injected with saline or scrambled ODNs including performing more 360 degrees turns to the left than to the right. There was significantly less **GABA** -stimulated Cl uptake in right striatum compared to left striatum of ASODN-**treated** rats with no significant difference between sides in control animals. Specific binding to benzodiazepine and convulsant sites on the GABAA receptor was not selectively altered by ASODN **treatment**. Combined alpha 2 beta 3 ASODN **treatment** did not affect either cocaine sensitivity or GABAA receptor function. There was no difference between the density of Nissl stained cells in the left and right edges of striatum in control or ASODN-

treated rats indicating the absence of significant neurotoxic effects of the ASODN **treatment**. Injection of fluorescein-conjugated ASODNs indicated that ASODN is present in striatum at times during which behavioral and neurochemical indices of **GABA** receptor function are decreased. Thus, the functional status of GABAA receptors in striatum may be involved in determining cocaine sensitivity.

5/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09612420 98387216
GABA(B)R1a/R1b-type receptor **antisense** deoxynucleotide **treatment** of melanotropes blocks chronic **GABA** (B) receptor inhibition of high voltage-activated Ca2+ channels.
Morris SJ; Beatty DM; Chronwall BM
Division of Molecular Biology and Biochemistry, School of Biological Sciences, University of Missouri-Kansas City, 64110-2499, USA.
Journal of neurochemistry (UNITED STATES) Sep 1998, 71 (3) p1329-32, ISSN 0022-3042 Journal Code: JAV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
GABA (B) and dopamine D2 receptors, both of which acutely inhibit adenylyl cyclase and high voltage-activated Ca2+ channels (HVA-CCs), are found in high levels in the melanotrope cells of the pituitary intermediate lobe. Chronic D2 receptor agonist application in vitro has been reported to result in inhibition of HVA-CC activity by down-regulation. Here we report that chronic **GABA**(B), but not **GABA**(A), agonist **treatment** also resulted in HVA-CC inhibition. Two **GABA**(B) receptor variants have been cloned and shown to inhibit adenylyl cyclase in HEK-293 cells. We have constructed an **antisense** deoxynucleotide knockdown-type probe that is complementary to 18 bp from the point at which the two sequences first become homologous. Chronic coincubation with baclofen and **GABA** (B) **antisense** nucleotide completely eliminated the inhibition of the channels by baclofen alone but had no reversing effect on HVA-CC inhibition by the D2 agonist quinpirole. A scrambled, missense nucleotide also had no reversing effect. Incubation with a D2 **antisense** knockdown probe eliminated the ability of a D2 agonist to inhibit the channels but had no effect on baclofen blockade. These results show the existence an R1a/R1b type of **GABA**(B) receptor, which, like the D2 receptor, is coupled to chronic HVA-CC inhibition in melanotropes.

5/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09597116 98363708
Protein kinase C regulates the interaction between a **GABA** transporter and syntaxin 1A.
Beckman ML; Bernstein EM; Quick MW
Department of Neurobiology, University of Alabama at Birmingham, Birmingham, Alabama 35294-0021, USA.
Journal of neuroscience (UNITED STATES) Aug 15 1998, 18 (16) p6103-12, ISSN 0270-6474 Journal Code: JDF
Contract/Grant No.: DA-10509, DA, NIDA
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Syntaxin 1A inhibits **GABA** uptake of an endogenous **GABA** transporter in neuronal cultures from rat hippocampus and in reconstitution systems expressing the cloned rat brain **GABA** transporter GAT1. Evidence of interactions between syntaxin 1A and GAT1 comes from three experimental approaches: botulinum toxin cleavage of syntaxin 1A, syntaxin 1A **antisense treatments**, and coimmunoprecipitation of a complex

containing GAT[redacted] and syntaxin 1A. Protein kinase C (PKC), shown previously to modulate GA[redacted] transporter function, exerts [redacted] modulatory effects by regulating the availability of syntaxin 1A to interact with the transporter, and a transporter mutant that fails to interact with syntaxin 1A is not regulated by PKC. These results suggest a new target for regulation by syntaxin 1A and a novel mechanism for controlling the machinery involved in both neurotransmitter release and reuptake.

5/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09461292 98186690
Effect of injection of **antisense** oligodeoxynucleotides of **GAD** isozymes into rat ventromedial hypothalamus on food intake and locomotor activity.
Bannai M; Ichikawa M; Nishihara M; Takahashi M
Department of Veterinary Physiology, Veterinary Medical Science, The University of Tokyo, Bunkyo-ku, Tokyo 113, Japan.
Brain research (NETHERLANDS) Feb 16 1998, 784 (1-2) p305-15, ISSN 0006-8993 Journal Code: B5L
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In the ventromedial hypothalamus (VMH), gamma-aminobutyric acid (**GABA**) plays a role in regulating feeding and running behaviors. The **GABA** synthetic enzyme, glutamic acid decarboxylase (**GAD**), consists of two isozymes, **GAD65** and **GAD67**. In the present study, the phosphorothioated **antisense** oligodeoxynucleotides (ODNs) of each **GAD** isozyme were injected bilaterally into the VMH of male rats, and food intake, body weight and locomotor activity were monitored. ODNs were incorporated in the water-absorbent polymer (WAP, 0.2 nmol/microliter) so that ODNs were retained at the injection site. Each **antisense** ODN of **GAD65** or **GAD67** tended to reduce food intake on day 1 (day of injection=day 0) though not significantly. An injection combining both **antisense** ODNs significantly decreased food intake only on day 1, but body weight remained significantly lower than the control for 5 days. This suppression of body weight gain could be attributed to a significant increase in locomotor activity between days 3 and 5. Individual **treatment** with either ODNs did not change locomotor activity. The increase in daily locomotor activity in the group receiving the combined **antisense** ODNs occurred mainly during the light phase. Neither vehicle (WAP) nor control ODN affected food intake, body weight and locomotor activity. Histological studies indicated that **antisense** ODN distributed within 800 micron from the edge of the area where WAP was located 24 h after the injection gradually disappeared within days, but still remained within 300 micron m distance even 7 days after the injection. **Antisense** ODN was effectively incorporated by all the cell types examined, i.e., neurons, astrocytes and microglias. Further, HPLC analysis revealed that **antisense** ODNs of **GAD** isozymes, either alone or combined, decreased the content of **GABA** by 50% in VMH 24 h after the injection. These results indicate that suppression of **GABA** synthesis by either of the **GAD** isozymes is synergistically involved in suppressing food intake and enhancing locomotor activity in rat VMH.

5/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09441517 98157936
Effects of peripheral-type benzodiazepine receptor **antisense** knockout on MA-10 Leydig cell proliferation and steroidogenesis.
Kelly-Hershkovitz E; Weizman R; Spanier I; Leschiner S; Lahav M;

Weisinger G; Gavish M
Department of Pharmacology, The Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, 31096 Haifa, Israel.
Journal of biological chemistry (UNITED STATES) Mar 6 1998, 273 (10) p5478-83, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The peripheral-type benzodiazepine receptor (PBR) is not only widely expressed throughout the body, but it is also genetically conserved from bacteria to humans. Many functions have been attributed to it, but its primary role remains a puzzle. In the current study, we stably transfected cultures of MA-10 Leydig cells with either control or 18-kDa PBR **antisense** knockout plasmids. The **antisense** knockout vector was driven by the human enkephalin promoter, which contains two cAMP response elements, such that cAMP **treatment** of transfected cells could superinduce 18-kDa PBR **antisense** RNA transcription and, hence, down-regulate endogenous 18-kDa PBR mRNA levels. Control and knockout MA-10 cell lines were then compared at the level of receptor binding, thymidine incorporation, and steroid biosynthesis. Eighteen-kilodalton PBR knockout reduced the maximal binding capacity of tritium-labeled PBR ligands, and the affinity of receptors to the ligands remained unaltered. Additionally, 24-h accumulation of progesterone was lower in the knockout cells. Exposure of the two cell types to 8-bromo-cAMP resulted in a robust increase in steroid production. However, a complex pattern of steroid accumulation was observed, in which further progestin metabolism was indicated. The later decline in accumulated progesterone as well as the synthesis of androstenedione were different in the two cell types. At the level of cell proliferation, reduction of 18-kDa PBR mRNA showed no effect. Thus, we conclude that the 18-kDa PBR may have a more important role in steroidogenesis than in proliferation in this Leydig cell line.

5/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09440687 98141033

Differential changes in induced seizures after hippocampal **treatment** of rats with an **antisense** oligodeoxynucleotide to the **GABA** (A) receptor gamma2 subunit [published erratum appears in Eur J Pharmacol 1998 Apr 24;347(2-3):367]

Karle J; Laudrup P; Sams-Dodd F; Mikkelsen JD; Nielsen M
The Research Institute of Biological Psychiatry, St. Hans Hospital, Roskilde, Denmark.
European journal of pharmacology (NETHERLANDS) Dec 11 1997, 340 (2-3) p153-60, ISSN 0014-2999 Journal Code: EN6
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Gamma-aminobutyric acid (**GABA**) is the principal inhibitory neurotransmitter in the brain. Impairment of GABAergic neurotransmission may be involved in the pathogenesis of epileptic phenomena. We have previously characterized biochemical and histological changes following unilateral intrahippocampal infusion of a phosphorothioate **antisense** oligodeoxynucleotide to the **GABA**(A) receptor gamma2 subunit in rats in vivo. The aim of the present study was to investigate the behavioral changes of rats following unilateral hippocampal **antisense** 'knockdown' of the **GABA**(A) receptor gamma2 subunit. **Antisense**, but not mismatch control oligodeoxynucleotide **treated** rats had a significant weight loss (10%) during 6 d of **treatment**. **Antisense treated** rats exhibited no changes in spontaneous behavior, including anxiety-like behavior as measured in the social interaction test, compared to mismatch oligodeoxynucleotide **treated** rats. However, **antisense treated** rats developed pronounced changes in induced seizure activity. Seizures induced by subcutaneously injected pentylenetetrazol were markedly accentuated in **antisense**

treated rats compared to **treatment** naive rats, whereas mismatch **treated** rats showed a lower seizure score than that of naive rats. **Antisense treated** rats had a significantly elevated threshold for seizures induced by electrical stimulation in the maximal electroshock seizure threshold test. The results suggest that intrahippocampal infusion of **antisense** oligodeoxynucleotide to the **GABA** (A) receptor gamma2 subunit leads to specific alterations in the sensitivity to induced seizures. The results are viewed as consequences of selective down-regulation of **GABA** (A) receptors and diminished inhibitory neurotransmission in the hippocampus.

5/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09292030 97454315

Diazepam protects against rat hippocampal neuronal cell death induced by **antisense** oligodeoxynucleotide to **GABA** (A) receptor gamma2 subunit.

Karle J; Witt MR; Nielsen M
Research Institute of Biological Psychiatry, St. Hans Hospital, Roskilde, Denmark. resshh@inet.uni-c.dk

Brain research (NETHERLANDS) Aug 8 1997, 765 (1) p21-9, ISSN 0006-8993 Journal Code: B5L
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Antisense oligodeoxynucleotides (ODNs) are used for the selective inhibition of gene expression. **Antisense** ODNs are promising tools for the investigation of physiological implications of proteins in the central nervous system of rodents in vivo. We have previously demonstrated that a phosphorothioate **antisense** ODN to the **GABA**(A) receptor gamma2 subunit, but not sense or mismatch control ODNs, induces a decrease in ex vivo benzodiazepine receptor radioligand binding in rat hippocampus when infused into the hippocampus in vivo [Karle et al., Neurosci. Lett., 202 (1995) 97-100]. This effect is parallelled by a decrease in the number of **GABA** (A) receptors and an extensive loss of hippocampal neurones. There is increasing awareness of risks of toxic 'non-**antisense**' effects induced by ODNs, and in particular phosphorothioate ODNs. The present experiments were designed to investigate the specificity of effects induced by the gamma2 subunit **antisense** ODN. The temporal development of changes in [3H]flunitrazepam and [3H]quinuclidinyl benzilate binding as well as in tissue protein levels supports the notion that the **antisense** ODN primarily acts by blocking the expression of the targeted receptor subunit protein. Furthermore, it is shown that a threshold for the elicitation of neurodegenerative changes exists. Finally, it is demonstrated that diazepam **treatment** of rats protects against the development of neuronal cell death induced by the **antisense** ODN. Collectively, the results support the hypothesis that the neurodegeneration induced by the **antisense** ODN is a consequence of diminished GABAergic inhibitory tonus following a selective down-regulation of gamma2 subunit-containing **GABA**(A) receptor complexes.

5/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09160062 97270292

Antisense oligonucleotides induce functional deletion of ligand gated ion channels in cultured neurons and brain explants.

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Graduate School Neurosciences Amsterdam, Research Institute Neurosciences Vrije Universiteit, Biological Faculty, The Netherlands.

Journal of neuroscience methods (NETHERLANDS) Jan 1997, 71 (1) p55-64,

ISSN 0165-0270 Journal Code: K9V
Languages: EN[redacted]SH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
The in situ application of the **antisense** technique for the study of ligand gated channels is discussed here. Using **antisense** oligodeoxynucleotides to downregulate a gene of interest means being confronted with a number of choices that will determine the success. These include choosing a target sequence, considering chemical modifications of the oligo as well as its length and estimation of the turnover of the target protein in order to set up the **treatment** schedule. In this paper a short overview of technical aspects of the **antisense** approach on primary cultured neurons and brain slice cultures is presented. In addition, the effects of **antisense** oligos on the expression of neuronal nicotinic acetylcholine receptors and **GABA**(A) receptors are discussed: Patch-clamp recordings of neurons **treated** with specific **antisense** oligos targeted at individual subunits showed a clear downregulation of the expression of native ligand gated channels. Moreover, in a number of experiments novel channel types with altered properties were observed following **antisense treatment** . Thus, non-targeted channel subunits that remain expressed after **antisense** deletion, may aggregate to form novel channel types that are normally not present. Alternatively, the translational arrest of a protein may be accompanied by compensatory changes in the synthesis and/or targeting of other channel subunits to the cell surface. The **antisense** technique enables identification of the functional contribution of individual channel subunits to endogenous channel activity in the central nervous system. As such it paves the way to the elucidation of in vivo channel-subunit composition and channel functions, of post- as well as pre-synaptic ligand gated channel receptors.

5/3,AB/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08896104 96233196
Cocaine selectively alters neurotransmitter receptor mRNAs in mouse embryos.
Mackler SA; Bennett GD; Tsuei VP; Finnell RH
Division of General Internal Medicine, University of Pennsylvania, Philadelphia, USA.
Reproductive toxicology (UNITED STATES) Jan-Feb 1996, 10 (1) p37-42,
ISSN 0890-6238 Journal Code: BE4
Contract/Grant No.: ES07165, ES, NIEHS; DE11303, DE, NIDCR; DA00199, DA, NIDA
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Alterations in gene expression due to in utero cocaine exposure may adversely affect nervous system development. The present study examined whether or not cocaine administration to pregnant mice alters embryonic mRNA levels for several developmentally-regulated genes. **Antisense** RNA amplification was performed using RNA from LM/Bc embryos at gestational days 9.5 and 10.5 after three days of cocaine **treatment**. This technique highlights simultaneous changes that occur in the expression of many genes after a teratogenic insult. Significant changes occurred in the expression pattern on only four genes from a total of 42 candidate cDNAs. These included increases in the relative levels of the alpha and beta 1 subunits of the GABAA receptor without concurrent changes in the non-NMDA glutamate receptor subunits. The results support the hypothesis that in utero cocaine exposure leads to specific changes in gene expression that may ultimately contribute to developmental abnormalities.

5/3,AB/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08892148 97098533

Intrastriatally injected c-fos **antisense** oligonucleotide interferes with striatonigral but not striatopallidal gamma-aminobutyric acid transmission in the conscious rat.

Sommer W; Rimondini R; O'Connor W; Hansson AC; Ungerstedt U; Fuxe K
Department of Neuroscience, Karolinska Institute, Stockholm, Sweden.

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Nov 26 1996, 93 (24) p14134-9, ISSN 0027-8424
Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Antisense c-fos oligonucleotides injected into the neostriatum of conscious rats selectively inhibited c-fos expression associated with compensatory increases in striatal c-fos mRNA levels and also with increased expression of junB and NGFI-A mRNA, probably as a result of regulatory phenomena. Dual probe in vivo microdialysis was used to investigate gamma-aminobutyric acid (**GABA**) release in the substantia nigra and the globus pallidus, which represent the terminal sites of the dopamine D1 receptor regulated striatonigral and the dopamine D2 receptor regulated striatopallidal **GABA** pathways, respectively. Intrastriatal infusion of the c-fos **antisense** oligonucleotide profoundly decreased dialysate **GABA** levels in the ipsilateral substantia nigra within 60 min but did not influence the dialysate **GABA** levels in the globus pallidus compared with the sham and control oligonucleotide **treated** groups. The site of action of the **antisense** oligonucleotides was mainly restricted to striatal neurons as shown by the distribution of locally injected fluoresceine isothiocyanate and radiolabeled oligonucleotides. The findings demonstrate a facilitatory role for c-fos mediated gene regulation in striatonigral **GABA** transmission and strengthen the evidence that the regulation of neurotransmission is different in the striatonigral and striatopallidal **GABA** pathways.

5/3,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08838771 96408608

Treatment with an **antisense** oligodeoxynucleotide to the GABAA receptor gamma 2 subunit increases convulsive threshold for beta-CCM, a benzodiazepine "inverse agonist', in rats.

Zhao TJ; Rosenberg HC; Chiu TH
Department of Pharmacology, Medical College of Ohio, Toledo 43699, USA.

European journal of pharmacology (NETHERLANDS) Jun 13 1996, 306 (1-3) p61-6, ISSN 0014-2999 Journal Code: EN6
Contract/Grant No.: DA02194, DA, NIDA
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The gamma 2 subunit of the gamma-aminobutyric acid type-A (GABAA) receptor is associated with the actions of benzodiazepines and related drugs. A phosphorothioate-modified **antisense** oligodeoxynucleotide directed against the gamma 2 subunit was given by i.c.v. injection (18 micrograms in 2 microliters saline) to male Sprague-Dawley rats every 12 h for 3 days. Controls received the corresponding sense oligodeoxynucleotide. 4-6 h after the last i.c.v. **treatment**, rats were given methyl-beta-carboline-3-carboxylate (beta-CCM), a benzodiazepine "inverse agonist', by slow i.v. infusion. Compared to naive rats, the beta-CCM threshold dose was not affected by the sense oligodeoxynucleotide, but was increased 87% in **antisense** oligodeoxynucleotide-**treated** rats. The **treatment** had no effect on the seizure threshold for picrotoxin. Both **antisense** and sense oligodeoxynucleotide **treatments** slightly increased the threshold for strychnine seizures. The results suggest that **antisense** oligodeoxynucleotide **treatment** altered

GABAA receptor composition and interfered with the actions of a benzodiazepine receptor ligand in vivo, and may provide a tool for studying regulation of receptor structure and function.

5/3,AB/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08741489 96295573
Alpha 6 and gamma 2 subunit **antisense** oligodeoxynucleotides alter gamma-aminobutyric acid receptor pharmacology in cerebellar granule neurons.
Zhu WJ; Wang JF; Vicini S; Grayson DR
Department of Psychiatry, Medical College of Pennsylvania, Pittsburgh, USA.
Molecular pharmacology (UNITED STATES) Jul 1996, 50 (1) p23-33, ISSN 0026-895X Journal Code: NGR
Contract/Grant No.: R01-NS30537, NS, NINDS; K04-NS01647, NS, NINDS; R01-NS32759, NS, NINDS; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE
To characterize the role of the alpha 6 subunit in gamma-aminobutyric acid (**GABA**) receptors in cerebellar granule cells, primary cerebellar cultures were **treated** with **antisense** oligodeoxynucleotides (ODNs) complementary to and overlapping the initial codon of the alpha 6 subunit cDNA. The specific reduction in the expression of the alpha 6 receptor subunit protein after a 48-hr **antisense** ODN **treatment** was assessed with the use of immunoblot assays. Sister cultures were **treated** in parallel with mismatched (scrambled) ODNs. Inhibition of **GABA** -gated currents by furosemide, a selective inhibitor of GABAA receptors containing alpha 6 subunits, was attenuated after the alpha 6 **antisense treatment** . Furosemide was tested in parallel in transfected cells expressing various combinations of the alpha 1 and alpha 6 subunits, which showed that the relative abundance of these subunit mRNAs determines the extent of furosemide-induced inhibition of **GABA**-gated currents. Compared with control or mismatched ODN-**treated** cell cultures, **treatment** of granule neurons with alpha 6 **antisense** ODNs caused a decrease in **GABA**-induced maximal current density and increased the half-maximal concentration derived from **GABA** dose-response curves. Furthermore, the depletion of alpha 6 subunits from cerebellar granule cells enhanced flunitrazepam-induced potentiation of **GABA**-activated currents. In contrast, gamma 2 **antisense** ODN **treatments** of cell cultures increased the receptor sensitivity to **GABA** and potently decreased the response to flunitrazepam. Our results show that alpha 6 and gamma 2 subunit expression can be blocked with the use of synthetic ODNs and that these subunits are crucial determinants of the pharmacological properties of native GABAA receptors in cerebellar granule cells.

5/3,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08538044 96379827
Antisense oligonucleotide to GABAA receptor gamma 2 subunit induces loss of neurones in rat hippocampus.
Karle J; Witt MR; Nielsen M
Research Institute of Biological Psychiatry, St. Hans Psychiatric Hospital, Roskilde, Denmark.
Neuroscience letters (IRELAND) Dec 29 1995, 202 (1-2) p97-100, ISSN 0304-3940 Journal Code: N7N
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The binding site for 1,4-benzodiazepines in the brain is part of the hetero-oligomeric gamma-aminobutyric acid (GABA) A receptor complex which regulates a chloride ion channel. The presence of the gamma 2 subunit in the complex is necessary for the binding of benzodiazepines to their binding site. This study demonstrates a reduction of benzodiazepine receptor radioligand binding by 43% compared to control following infusion of phosphorothioate **antisense** oligodeoxynucleotide to gamma 2 subunit into rat hippocampus. Reduction of benzodiazepine binding sites was paralleled by a decrease in [35S]tert-butyl-bicyclo-phosphorothionate ([35S]TBPS) binding (51%) and [3H]muscimol binding (37%), indicating a reduction in the number of GABAA receptors. Changed macroscopic appearance, reduced protein content and severe loss of neurones in **antisense-treated** hippocampi suggests that the reduced formation of GABAA receptors leads to neuronal cell death.

5/3,AB/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08504147 96087365
Effect of muscimol on haloperidol-induced alteration of neurotensin gene expression in the striatum and nucleus accumbens in the rat.
Decker KP; Roy-Byrne PP; Merchant KM
Harborview Medical Center, University of Washington, Seattle 98104, USA.
Brain research (NETHERLANDS) Sep 11 1995, 691 (1-2) p9-17, ISSN 0006-8993 Journal Code: B5L
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Acute neuroleptic administration increases the expression of neurotensin/neuromedin (NT/N) gene in rat dorsolateral striatum and shell sector of the nucleus accumbens. The purpose of this study was to examine modulation of neuroleptic induction of NT/N and the proto-oncogene c-fos expression by the GABAA agonist muscimol. Adult male Sprague-Dawley rats were **treated** with saline, haloperidol (1 mg/kg); muscimol (3.2 mg/kg); or haloperidol (1 mg/kg) plus muscimol (3.2 mg/kg). Animals were sacrificed 1 h after drug administration. Expression of NT/N and c-fos mRNA was examined by in situ hybridization using 35S-**antisense** probes. Muscimol alone had no measurable effect on basal levels of NT/N or c-fos mRNA in either the dorsolateral striatum or the nucleus accumbens. However, co-administration of muscimol with haloperidol reduced haloperidol-induced increases in NT/N as well as c-fos mRNA in the dorsolateral striatum. In contrast, NT/N mRNA expression in accumbal shell induced by haloperidol was not modulated by co-administration of muscimol. These data suggest that GABAA receptors may be involved in regulation of NT/N gene expression in the DLSt, but not in the nucleus accumbens.

5/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08501690 96129660
Insulin-like growth factor I is an afferent trophic signal that modulates calbindin-28kD in adult Purkinje cells.
Nieto-Bona MP; Busiguina S; Torres-Aleman I
Laboratory of Cellular and Molecular Neuroendocrinology, Cajal Institute, Consejo Superior de Investigaciones Cientificas, Madrid, Spain.
Journal of neuroscience research (UNITED STATES) Oct 15 1995, 42 (3) p371-6, ISSN 0360-4012 Journal Code: KAC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Recent evidence suggests that Purkinje cells are specific targets of insulin-like growth factor I (IGF-I) through their entire life span. During development, Purkinje cell numbers and their calbindin-28kD content

increase after IGF-I **treatment** in culture. In the adult, part of the IGF-I present in the cerebellum is transported from the inferior olive, and modulates Purkinje cell function. We investigated whether IGF-I produced by inferior olive neurons and transported to the contralateral cerebellum through climbing fibers may modulate the levels of calbindin-28kD in the cerebellum of adult animals. Twenty-four hr after injection of an **antisense** oligonucleotide of IGF-I into the inferior olive, both IGF-I and calbindin-28kD levels in the contralateral cerebellar lobe were significantly reduced, while the number of calbindin-positive Purkinje cells was unchanged. The effect of the **antisense** on IGF-I levels was fully reversed 3 days after its injection into the inferior olive, with a postinhibitory rebound observed at this time, while calbindin-28kD levels slowly returned to control values. A control oligonucleotide did not produce any change in either IGF-I or calbindin-28kD content in the cerebellum. These results indicate that normal levels of IGF-I in the inferior olive are necessary to maintain appropriate levels of IGF-I in the cerebellum and of calbindin-28kD in the Purkinje cell. These results also extend our previous findings on the existence of an olivo-cerebellar IGF-I-containing pathway with trophic influence on the adult Purkinje cell.

5/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08373809 95388262

Antisense oligonucleotide-induced block of individual GABAA receptor alpha subunits in cultured visual cortex slices reduces amplitude of evoked inhibitory postsynaptic currents.

Brussaard AB; Baker RE

Graduate School Neurosciences Amsterdam, Research Institute Neurosciences, Vrije Universiteit, Faculty of Biology, The Netherlands.

Neuroscience letters (IRELAND) May 19 1995, 191 (1-2) p111-5, ISSN 0304-3940 Journal Code: N7N

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Whole cell patch clamp recordings were made in layer II-IV from organotypic slices of rat primary visual cortex, explanted at postnatal day 6 and maintained in a serum-free medium. Neurons evinced current clamp characteristics typical for stellate cells. Between 7 and 21 days in culture, both glutamate- and **GABA**-mediated postsynaptic currents were observed. Long-term culturing in the presence of a degenerate 15-mer **antisense** oligonucleotide directed against the transcripts of all alpha subunits genes of the GABAA receptor resulted in a dose dependent reduction of evoked **GABA** synaptic currents. This reduction was maximal (80%) at 20 microM. A randomized control oligo had no effect. Evoked glutamatergic excitatory postsynaptic currents were unaffected following oligo **treatment**. A 15-mer **antisense** oligo directed against the alpha 1 subunit gave variable effects: in some cells the amplitude of evoked GABAergic inhibitory postsynaptic currents (IPSCs) was reduced by 50-75%, while in other cells recorded from the same slices, there was little or no effect. An **antisense** oligo, directed against the alpha 2 subunit, however, gave a consistent and robust 80% reduction of the amplitude of evoked IPSCs. A 15-mer 3-base mismatch oligo against alpha 2 had no effect. We conclude that the alpha 2 subunit functions in postsynaptic GABAA receptors located on or close to the cell bodies of stellate cells. The role of the alpha 1 subunit is less clear, but this subunit seems spatially differentiated. The in situ **antisense** oligo technique should provide further insight into the biophysical and pharmacological consequences of the subunit composition of ligand gated channels at functional synapses.

5/3,AB/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08273379 95235317

Basic fibroblast growth factor increases the number of excitatory neurons containing glutamate in the cerebral cortex.

Vaccarino FM; Schwartz ML; Hartigan D; Leckman JF

Child Study Center, Yale University, New Haven, Connecticut 06510, USA.

Cerebral cortex (UNITED STATES) Jan-Feb 1995, 5 (1) p64-78, ISSN 1047-3211 Journal Code: BI9

Contract/Grant No.: MH49351, MH, NIMH; MH30929, MH, NIMH; MH18268, MH, NIMH; +

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Stem cells isolated from the ventricular zone of embryonic day 12.5 rat telencephalon progressively proliferate and differentiate in vitro into three major classes of amino acid-containing neurons, glutamate, aspartate, and **GABA** . We quantitatively examined the effect of basic fibroblast growth factor (bFGF) and nerve growth factor (NGF) on amino acid-containing neurons. bFGF caused a threefold increase in glutamate-containing neurons, while the number of **GABA**- and aspartate-containing neurons was not significantly changed. In contrast, NGF did not alter the number of amino acid-containing neurons. The ratio of glutamate- to **GABA**-containing neurons in untreated or NGF-**treated** cultures was 0.6:1. In the bFGF-**treated** cultures, this ratio was 1.4:1, which closely approximates the ratio in the cerebral cortex in vivo. **Treatment** with **antisense** oligonucleotides targeted to bFGF mRNA provoked a 50% decrease in the number of glutamate-containing neurons but had no significant effect on the **GABA**-containing neurons. Thus, diffusible factors such as bFGF may play an important role in determining the relative proportion of excitatory versus inhibitory neurons in the cerebral cortex by selectively regulating the proliferation of stem cells committed to different neurotransmitter phenotypes.

5/3,AB/33 (Item 33 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

08192536 95157170

Expression of **GAD** mRNA in spinal cord neurons of normal and monoarthritic rats.

Castro-Lopes JM; Tolle TR; Pan B; Zieglgansberger W

Institute of Histology and Embryology, Faculty of Medicine of Oporto, Porto, Portugal.

Brain research. Molecular brain research (NETHERLANDS) Oct 1994, 26 (1-2) p169-76, ISSN 0169-328X Journal Code: MBR

Languages: ENGLISH

Document type: JOURNAL ARTICLE

This study was carried out to investigate whether the increase of **GABA** levels in spinal cord dorsal horn in response to chronic inflammatory lesions results from an enhanced expression of the gene that governs the production of glutamate decarboxylase (**GAD**), the enzyme responsible for **GABA** synthesis. In situ hybridization was used to visualize neurons expressing **GAD** mRNA within the spinal cord, in both intact rats and in animals bearing chronic monoarthritis induced by intraarticular injection of complete Freund's adjuvant. In control normal animals, neuronal labeling by an **antisense** oligonucleotide probe occurred throughout the spinal gray matter, except in the motoneuronal pool of Rexed's lamina IX. In **treated** animals 4 days after the induction of monoarthritis, a significant increase in the number of labeled cells occurred in the superficial laminae (25.3%) and the neck (17.2%) of the ipsilateral dorsal horn at segments L4-L5 which contain the projection domain of the ankle joint. At 2 weeks, values were, respectively, 20.2% and 13.9% over contralateral values, and an increase of 12.4% was found in the ventral horn. At 3 weeks, the ipsilateral increase of labeled cells was

restricted to the superficial dorsal horn (15.2%). These findings emphasize the role played by the spinal GABAergic system in the modulation of chronic nociceptive input. It is suggested that the response of the spinal GABAergic system depends on the activation of **GAD** gene transcription in spinal neurons.

5/3,AB/34 (Item 34 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08121471 95171630
Central neurons and neurotransmitters in the control of blood pressure.
Chalmers J; Arnolda L; Llewellyn-Smith I; Minson J; Pilowsky P; Suzuki S
Department of Medicine, Flinders Medical Centre, Adelaide, South Australia.
Clinical and experimental pharmacology & physiology (AUSTRALIA) Oct 1994, 21 (10) p819-29, ISSN 0305-1870 Journal Code: DD8
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
1. In this paper we review recent work from our laboratory on two major pathways important in the central control of blood pressure. 2. We report experiments on the sympatho-excitatory bulbospinal pathway from the rostral ventral medulla. Here we focus particularly on the role of excitatory amino acids. 3. We review studies on the short inhibitory or depressor pathway ascending from the caudal to the rostral ventral medulla, which is thought to use gamma-aminobutyric acid (**GABA**) as its neurotransmitter. We report on experiments with the immediate early gene, c-fos, demonstrating that its expression in the bulbospinal pressor neurons is increased by stimuli that activate these nerves, and that this expression can be blocked in vivo by **treatment** with an **antisense** oligonucleotide. We also show that basal and stimulated expression of the c-fos gene is important in the central control of blood pressure.

5/3,AB/35 (Item 35 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07989872 94350958
The polypeptide diazepam-binding inhibitor and a higher affinity mitochondrial peripheral-type benzodiazepine receptor sustain constitutive steroidogenesis in the R2C Leydig tumor cell line.
Garnier M; Boujrad N; Ogwuegbu SO; Hudson JR Jr; Papadopoulos V
Department of Cell Biology, Georgetown University Medical Center, Washington, D.C. 20007.
Journal of biological chemistry (UNITED STATES) Sep 2 1994, 269 (35) p22105-12, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: DK-43358, DK, NIDDK; HD-01031, HD, NICHD
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The polypeptide diazepam binding inhibitor (DBI) and drug ligands for the mitochondrial peripheral-type benzodiazepine receptor (PBR) have been shown to regulate cholesterol transport, the rate-determining step in steroidogenesis, in hormone-responsive steroidogenic cells including the MA-10 Leydig tumor cells. The present study was designed to characterize the role of DBI and PBR in the R2C rat Leydig tumor constitutive steroid-producing cell model. Both DBI and PBR were present in R2C cells. R2C cell **treatment** with a cholesterol-linked phosphorothioate oligodeoxynucleotide **antisense** to DBI, but not sense, resulted in the reduction of DBI levels and a concomitant dramatic decrease of the amount of progesterone produced. These observations strongly suggested that DBI was important in maintaining constitutive steroidogenesis in R2C cells. Radioligand binding assays revealed the presence of a single class of PBR binding sites with an affinity 10 times higher (Kd approximately 0.5 nM)

than that displaced by the MA-10 PBR (Kd approximately 5 nM). Photolabeling of R2C and MA-10 cell mitochondria with the photoactivatable PBR ligand [3H]1-(2-fluoro-5-nitrophenyl)-N-methyl-N-(1-methyl-propyl)-3- isoquinoline carboxamide showed that the M(r) 18,000 PBR protein was specifically labeled. This indicates that the R2C cells express a PBR protein which has properties similar to the MA-10 PBR. Chemical crosslinking studies of purified metabolically radiolabeled DBI to mitochondria provided direct evidence that DBI specifically binds to the M(r) 18,000 PBR protein. Moreover, DBI and a PBR synthetic ligand were able to increase steroid production in isolated R2C cell mitochondria which express the 5 nM affinity receptor. However, mitochondrial PBR binding was increased by 6-fold upon addition of the post-mitochondrial fraction, suggesting that a cytosolic factor modulates the binding properties of PBR in R2C cells and is responsible for the 0.5 nM affinity receptor seen in intact cells. In conclusion, these data demonstrate that DBI plays a key role in maintaining R2C constitutive steroidogenesis by binding to the mitochondrial higher affinity PBR which promotes a continuous supply of cholesterol to the inner mitochondrial side chain cleavage cytochrome P450.

5/3,AB/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07946115 94282571

Intracerebral administration of **antisense** oligodeoxynucleotides to **GAD65** and **GAD67** mRNAs modulate reproductive behavior in the female rat.

McCarthy MM; Masters DB; Rimvall K; Schwartz-Giblin S; Pfaff DW
Rockefeller University, Laboratory of Neurobiology and Behavior, New York, NY 10028.

Brain research (NETHERLANDS) Feb 14 1994, 636 (2) p209-20, ISSN 0006-8993 Journal Code: B5L
Contract/Grant No.: HD-05751, HD, NICHD
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Increased **GABA** activity in the medial hypothalamus (HYP) and midbrain central gray (MCG), but not the preoptic area (POA), facilitates sexual receptivity in the female rat [40]. In the current experiments, ovariectomized females were chronically **treated** with estrogen (via silastic capsules) to maintain a continuously high level of lordosis response. Administration of crystalline **antisense** oligodeoxynucleotid e to the **GABA** synthetic enzyme, **GAD67**, into the HYP and MCG significantly and reversibly reduced lordosis response for 1-2 days, but did not inhibit lordosis when administered into the POA. Administration of a control oligonucleotide, consisting of the same nucleotide bases but in a scrambled sequence, did not significantly modulate behavior when infused into any brain areas. When oligodeoxynucleotide **antisense** to **GAD67** was suspended in oil and then infused into the HYP or MCG it was more effective and resulted in less inter-animal variability. Subsequent experiments involving infusions into the MCG compared the effectiveness of **antisense** oligonucleotides to the two different forms of **GAD**, known as **GAD65** and **GAD67** . Oligodeoxynucleotides **antisense** to the mRNA for either gene were effective at reducing lordosis behavior but with a different time course. Oligonucleotide **antisense** to **GAD67** significantly reduced behavior within 24 h of infusion and there was full recovery by 4 days post-infusion. **GAD65** **antisense** oligonucleotide did not significantly reduce behavior until 48 h post infusion and animals did not fully recover to pretest levels of lordosis until 5 days post-infusion. When **antisense** oligonucleotide for the two genes was administered simultaneously, the inhibition of lordosis was maximal at 24 h and stayed depressed for 4 days. There did not appear to be an additive effect of the two different **antisense** oligonucleotides when administered together. Tissue **GABA** levels in HYP and MCG of individual rats assayed by HPLC

were no longer correlated with lordosis score after **antisense** oligonucleotide infusion but were after infusions of scrambled control oligos. Immunoblotting for the two forms of **GAD** revealed that **GAD67** **antisense** oligonucleotide infusion led to significant decreases in both **GAD67** and **GAD65** protein levels as compared to infusions of scrambled control oligo. In addition, the levels of a neuronal marker, neuron-specific enolase, also decreased (although nonsignificantly) suggesting either a temporary shutdown of protein synthesis or a degeneration of GABAergic neurons after **GAD67** **antisense** oligonucleotide infusion.

5/3,AB/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07624644 93140034

A specific **antisense** oligodeoxynucleotide to mRNAs encoding receptors with seven transmembrane spanning regions decreases muscarinic m2 and gamma-aminobutyric acidB receptors in rat cerebellar granule cells.

Holopainen I; Wojcik WJ
Fidia Georgetown Institute for the Neurosciences, Georgetown University, School of Medicine, Washington, D.C.

Journal of pharmacology and experimental therapeutics (UNITED STATES) Jan 1993, 264 (1) p423-30, ISSN 0022-3565 Journal Code: JP3
Contract/Grant No.: NS26990, NS, NINDS; MH 45223, MH, NIMH
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Many receptors that inhibit adenylyl cyclase belong to a common superfamily of receptors that couple to guanine nucleotide binding proteins. These receptors are thought to span the membrane seven times and to have a highly homologous amino acid sequence (LACADL) in the second membrane spanning region. The **antisense** oligodeoxynucleotide seven-transmembrane spanning receptor (7TMR), a 15-mer that binds to mRNA encoding this amino acid sequence, was added to cerebellar granule neuron cultures to decrease receptors of this superfamily. Intact **antisense** 7TMR was found to enter neurons. This 4- to 6-day **treatment** with **antisense** oligonucleotide decreased the total number of muscarinic receptor binding sites by about 40% and completely eliminated muscarinic m2 receptors that inhibit cyclic AMP formation. **Antisense** 7TMR **treatment** at 25 microM prevented the gamma-aminobutyric acid (**GABA**)B-mediated inhibition of cyclic AMP formation by about 40%. The **treatment** was effective in decreasing GABAA receptors only when the **antisense** oligonucleotide was given 1 day after plating the cells, and the receptor response assay was performed 6 days later. The half-maximal concentration of **antisense** 7TMR was approximately 5 microM in blocking GABAB receptors. **Antisense** 7TMR appeared to be specific because another **antisense** oligodeoxynucleotide sequence (15-mer) having four mismatches with 7TMR had no effect on either muscarinic m2 or GABAB receptor-mediated responses and did not affect the total number of muscarinic binding sites. These results are consistent with the view that **antisense** oligonucleotides decrease proteins in which the nucleotide sequence is known such as the muscaranic m2 receptor.(ABSTRACT TRUNCATED AT 250 WORDS)

5/3,AB/38 (Item 38 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07326427 92408434

Expression of glutamic acid decarboxylase messenger RNA in rat medial preoptic area neurones during the oestrous cycle and after ovariectomy.

Herbison AE; Augood SJ; McGowan EM
Department of Neuroendocrinology, AFRC Institute of Animal Physiology and

Genetics Resea[redacted] Babraham, Cambridge, UK.
Brain resea[redacted]. Molecular brain research ([redacted]HERLANDS) Aug 1992, 14 (4) p310-6, ISSN 0169-328X Journal Code: MBR
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Evidence suggests that medial preoptic area (MPOA) neurones containing gamma-aminobutyric acid (**GABA**) are modulated directly by oestrogen. We have used an alkaline phosphatase-labelled **antisense** oligonucleotide probe to examine glutamic acid decarboxylase67 (**GAD**) mRNA expression within individual cells of the MPOA, diagonal band of Broca (DBB) and parietal cortex in rats killed at noon on each day of the oestrous cycle and after ovariectomy (n = 4-5). As a fall in extracellular **GABA** concentrations occurs in the MPOA on the afternoon of proestrus, the **GAD67** mRNA content of cells was also examined in proestrous rats at 15:00h immediately prior to the preovulatory luteinising hormone (LH) surge. The MPOA was found to have an intermediate number of **GAD67** mRNA-containing cells compared with the DBB and cortex (P less than 0.01) but expressed the lowest mean hybridisation signal (P less than 0.01). The parietal cortex had significantly fewer (P less than 0.01) **GAD** mRNA-containing cells than either the MPOA or DBB but these contained higher mean density of signal (P less than 0.01). The hybridisation signal for **GAD** mRNA was abolished by either ribonuclease pre-**treatment** or the use of excess non-labelled probe. No significant (P greater than 0.05) differences in **GAD67** mRNA were detected in animals killed at noon throughout the oestrous cycle or after ovariectomy. On the afternoon of proestrus (15:00h) there was a significant 40% reduction in mean **GAD67** mRNA content within cells of only the MPOA compared with noon (P less than 0.05). The numbers of cells in the MPOA expressing **GAD67** mRNA were not significantly different.(ABSTRACT TRUNCATED AT 250 WORDS)

5/3,AB/39 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12744899 BIOSIS NO.: 200000498522
Decreasing **GAD** neonatally attenuates steroid-induced sexual differentiation of the rat brain.
AUTHOR: Davis Aline M; Grattan David R; McCarthy Margaret M(a)
AUTHOR ADDRESS: (a)Department of Physiology, University of Maryland School of Medicine, 655 West Baltimore Street, Baltimore, MD, 21201**USA
JOURNAL: Behavioral Neuroscience 114 (5):p923-933 October, 2000
MEDIUM: print
ISSN: 0735-7044
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: During development, exposure to gonadal steroids results in brain sexual differentiation. Postnatally, hypothalamic gamma-aminobutyric acid (**GABA**) levels are almost double in males versus females. We hypothesized that increased **GABA** neonatally results in masculinization. Males, females, and androgenized females were infused intrahypothalamically with **antisense** oligonucleotides against glutamic acid decarboxylase (**GAD**) mRNA at birth to reduce **GABA** synthesis. **GAD** protein and **GABA** levels were reduced 24 hr later without obvious toxic effects, as determined by histological examination. As adults, neonatally **antisense-treated**, androgenized females showed reduced intromission-like behavior and lordosis quotients compared with vehicle and scrambled controls. Lordosis quotients were reduced about 50% in nonandrogenized females versus vehicle and scrambled controls. These data suggest that **GABA** is involved in mediating brain sex differentiation and may act in both males and females.

5/3,AB/40 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11625583 BIOSIS NO.: 199800407925
Protein kinase C regulates the interaction between a **GABA** transporter and syntaxin A.
AUTHOR: Beckman Matthew L; Bernstein Eve M; Quick Michael W(a)
AUTHOR ADDRESS: (a)Dep. Neurobiol., CIRC 446, 1719 Sixth Ave. S., Birmingham, AL 35294-0021**USA
JOURNAL: Journal of Neuroscience 18 (16):p6103-6112 Aug. 15, 1998
ISSN: 0270-6474
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Syntaxin 1A inhibits **GABA** uptake of an endogenous **GABA** transporter in neuronal cultures from rat hippocampus and in reconstitution systems expressing the cloned rat brain **GABA** transporter GAT1. Evidence of interactions between syntaxin 1A and GAT1 comes from three experimental approaches: botulinum toxin cleavage of syntaxin 1A, syntaxin 1A **antisense treatments**, and coimmunoprecipitation of a complex containing GAT1 and syntaxin 1A. Protein kinase C (PKC), shown previously to modulate **GABA** transporter function, exerts its modulatory effects by regulating the availability of syntaxin 1A to interact with the transporter, and a transporter mutant that fails to interact with syntaxin 1A is not regulated by PKC. These results suggest a new target for regulation by syntaxin 1A and a novel mechanism for controlling the machinery involved in both neurotransmitter release and reuptake.

5/3,AB/41 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11317178 BIOSIS NO.: 199800098510
Differential changes in induced seizures after hippocampal **treatment** of rats with an **antisense** oligodeoxynucleotide to the GABAA receptor gamma2 subunit.
AUTHOR: Karle Jesper(a); Laudrup Peter; Sams-Dodd Frank; Mikkelsen Jens D; Nielsen Mogens
AUTHOR ADDRESS: (a)Dep. Psychiatry, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen O**Denmark
JOURNAL: European Journal of Pharmacology 340 (2-3):p153-160 Dec. 11, 1997
ISSN: 0014-2999
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: gamma-Aminobutyric acid (**GABA**) is the principal inhibitory neurotransmitter in the brain. Impairment of GABAergic neurotransmission may be involved in the pathogenesis of epileptic phenomena. We have previously characterized biochemical and histological changes following unilateral intrahippocampal infusion of a phosphorothioate **antisense** oligodeoxynucleotide to the GABAA receptor gamma2 subunit in rats in vivo. The aim of the present study was to investigate the behavioral changes of rats following unilateral hippocampal **antisense** 'knockdown' of the GABAA receptor gamma2 subunit. **Antisense**, but not mismatch control oligodeoxynucleotide **treated** rats had a significant weight loss (10%) during 6 d of **treatment**. **Antisense treated** rats exhibited no changes in spontaneous behavior, including anxiety-like behavior as measured in

the social interaction test, compared to mismatch oligodeoxynucleotide **treated** rats. However, **antisense treated** rats developed pronounced changes in induced seizure activity. Seizures induced by subcutaneously injected pentylenetetrazol were markedly accentuated in **antisense treated** rats compared to **treatment** naive rats, whereas mismatch **treated** rats showed a lower seizure score than that of naive rats. **Antisense treated** rats had a significantly elevated threshold for seizures induced by electrical stimulation in the maximal electroshock seizure threshold test. The results suggest that intrahippocampal infusion of **antisense** oligodeoxynucleotide to the GABAA receptor gamma2 subunit leads to specific alterations in the sensitivity to induced seizures. The results are viewed as consequences of selective down-regulation of GABAA receptors and diminished inhibitory neurotransmission in the hippocampus.

5/3,AB/42 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10121377 BIOSIS NO.: 199698576295
Antisense oligonucleotide inhibition of **GABA**-A receptor mRNA increases cocaine sensitivity in rats.
AUTHOR: Wielbo Donna(a); Peris Joanna
AUTHOR ADDRESS: (a)Dep. Pharmaceutics, Univ. Florida, Gainesville, FL 32610 **USA
JOURNAL: Pharmaceutical Research (New York) 12 (9 SUPPL.):pS405 1995
CONFERENCE/MEETING: Annual Meeting of the American Association of Pharmaceutical Scientists Miami Beach, Florida, USA November 5-9, 1995
ISSN: 0724-8741
RECORD TYPE: Citation
LANGUAGE: English

5/3,AB/43 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE

10710245 EMBASE No: 2000198754
Antidepressant effects on **GABA**-stimulated sup 3sup 6Clsup - influx in rat cerebral cortex are altered after **treatment** with **GABA**(A) receptor **antisense** oligodeoxynucleotides
Malatynska E.; Crites G.J.; Harrawood D.; Goldenberg R.; Matheson G.K.
E. Malatynska, Dept. Pharmacology and Toxicology, Indiana University School Medicine, 8600 University Boulevard, Evansville, IN 47712 United States
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Brain Research (BRAIN RES.) (Netherlands) 30 JUN 2000, 869/1-2 (78-84)
CODEN: BRREA ISSN: 0006-8993
PUBLISHER ITEM IDENTIFIER: S0006899300023544
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 31

Antidepressants act at the **GABA**(A) receptor to inhibit **GABA** -stimulated sup 3sup 6Clsup - influx and **GABA** reduction of [sup 3sup 5S]TBPS binding. This study examined how selective knock-down (via **antisense** oligodeoxynucleotides, aODNs) of **GABA**(A) receptor subunits modified antidepressant activity. The specific aODNs used were for the alpha1, beta1, beta2 or gamma2 subunits of the **GABA**(A) receptor. The aODN microinjections reduced corresponding **GABA**(A) receptor subunit mRNA levels by 30-40% as assessed by RT-PCR. The inhibitory effect of the antidepressants amitriptyline and mianserin on **GABA**-stimulated sup 3sup 6Clsup - influx was decreased after microinjections of alpha1, beta1, or beta2 subunit aODNs but potentiated after microinjections of

gamma2 subunit aODNs. This pattern of aODNs effect on amitriptyline and mianserin modulation of **GABA**-stimulated sup 3sup 6Clsup - influx was the same for both antidepressants and similar to **GABA** but different than that of diazepam and bicuculline. We conclude that multiple subunits of the **GABA**(A) receptor regulate the effect of amitriptyline and mianserin on the **GABA**(A) receptor chloride ionophore complex. However, the exact identity of the subunit mediating the direct or allosteric modulation of the antidepressant effect on **GABA**-stimulated sup 3sup 6Clsup - influx remains unclear. Theme: Neurotransmitters, modulators, transporters, and receptors. Topic: **GABA** receptors.

5/3,AB/44 (Item 2 from file: 72)
DIALOG(R)File 72:EMBASE

07877346 EMBASE No: 1999357992
Effects of **treatment** with **GABA**(A) receptor subunit **antisense** oligodeoxynucleotides on **GABA**-stimulated sup 3sup 6Clsup - influx in the rat cerebral cortex
Malatynska E.; Matheson G.K.; Goldenberg R.; Crites G.J.; Schindler N.L.; Weinzapfel D.; Harrawood D.; Yochum A.; Tunnicliff G.
E. Malatynska, Dept. Pharmacology and Toxicology, Indiana University, School of Medicine, Evansville, IN 47712 United States
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Neurochemistry International (NEUROCHEM. INT.) (United Kingdom) 2000, 36/1 (45-54)
CODEN: NEUID ISSN: 0197-0186
PUBLISHER ITEM IDENTIFIER: S019701869900100X
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 39

GABA(A) receptor function was studied in cerebral cortical vesicles prepared from rats after intracerebroventricular microinjections of **antisense** oligodeoxynucleotides (aODNs) for alpha1, gamma2, beta1, beta2 subunits. **GABA**(A) receptor alpha1 subunit aODNs decreased alpha1 subunit mRNA by 59+/-10%. Specific [sup 3H]**GABA** binding was decreased by alpha1 or beta2 subunit aODNs (to 63+/-3% and 64+/-9%, respectively) but not changed by gamma2 subunit aODNs (94+/-5%). Specific [sup 3H]flunitrazepam binding was increased by alpha1 or beta2 subunit aODNs (122+/-8% and 126+/-11%, respectively) and decreased by gamma2 subunit aODNs (50+/-13%). The 'knockdown' of specific subunits of the **GABA**(A) receptor significantly influenced **GABA**-stimulated sup 3sup 6Clsup - influx. Injection of alpha1 subunit aODNs decreased basal sup 3sup 6Clsup - influx and the **GABA** E(max); enhanced **GABA** modulation by diazepam; and decreased antagonism of **GABA** activity by bicuculline. Injection of gamma2 subunit aODNs increased the **GABA** E(max); reversed the modulatory efficacy of diazepam from enhancement to inhibition of **GABA**-stimulation; and reduced the antagonist effect of bicuculline. Injection of beta2 subunit aODNs reduced the effect of diazepam whereas **treatment** with beta1 subunit aODNs had no effect on the drugs studied. Conclusions from our studies are: (1) alpha1 subunits promote, beta2 subunits maintain, and gamma2 subunits suppress **GABA** stimulation of sup 3sup 6Clsup - influx; (2) alpha1 subunits suppress, whereas beta2, and gamma2 subunits promote allosteric modulation by benzodiazepines; (3) diazepam can act as an agonist or inverse agonist depending on the relative composition of the receptor subunits; and (4) the mixed competitive/non-competitive effects of bicuculline result from activity at alpha1 and gamma2 subunits and the lack of activity at beta1 and beta2 subunits. Copyright (C) 1999 Elsevier Science Ltd.

5/3,AB/45 (Item 3 from file: 72)

DIALOG(R)File [redacted]EMBASE
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07387156 EMBASE No: 1998286559
GABA(B)R1a/R1b-type receptor **antisense** deoxynucleotide **treatment** of melanotropes blocks chronic **GABA**(B) receptor inhibition of high voltage- activated Casup 2sup + channels
Morris S.J.; Beatty D.M.; Chronwall B.M.
Dr. S.J. Morris, Div. of Molec. Biol./Biochemistry, School of Biological Sciences, University of Missouri, 5007 Rockhill Road, Kansas City, MO 64110-2499 United States
Journal of Neurochemistry (J. NEUROCHEM.) (United States) 1998, 71/3 (1329-1332)
CODEN: JONRA ISSN: 0022-3042
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 34

GABA(B) and dopamine Dinf 2 receptors, both of which acutely inhibit adenylyl cyclase and high voltage-activated Casup 2sup + channels (HVA-CCs), are found in high levels in the melanotrope cells of the pituitary intermediate lobe. Chronic Dinf 2 receptor agonist application in vitro has been reported to result in inhibition of HVA-CC activity by down-regulation. Here we report that chronic **GABA**(B), but not **GABA**(A), agonist **treatment** also resulted in HVA-CC inhibition. Two **GABA**(B) receptor variants have been cloned and shown to inhibit adenylyl cyclase in HEK-293 cells. We have constructed an **antisense** deoxynucleotide knockdown-type probe that is complementary to 18 bp from the point at which the two sequences first become homologous. Chronic coincubation with baclofen and **GABA**(B) **antisense** nucleotide completely eliminated the inhibition of the channels by baclofen alone but had no reversing effect on HVA-CC inhibition by the Dinf 2 agonist quinpirole. A scrambled, missense nucleotide also had no reversing effect. Incubation with a Dinf 2 **antisense** knockdown probe eliminated the ability of a Dinf 2 agonist to inhibit the channels but had no effect on baclofen blockade. These results show the existence an R1a/R1b type of **GABA**(B) receptor, which, like the Dinf 2 receptor, is coupled to chronic HVA-CC inhibition in melanotropes.

5/3,AB/46 (Item 4 from file: 72)
DIALOG(R)File 72:EMBASE
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07295852 EMBASE No: 1998171206
Erratum: Differential changes in induced seizures after hippocampal **treatment** of rats with an **antisense** oligodeoxynucleotide to the **GABA**(A) receptor gamma2 subunit (European Journal of Pharmacology (1997) 340 (153- 160)): PII S0014299997014234
Karle J.; Laudrup P.; Sams-Dodd F.; Mikkelsen J.D.; Nielsen M.
J. Karle, Res. Inst. of Biological Psychiatry, St. Hans Hospital, DK-4000 Roskilde Denmark
European Journal of Pharmacology (EUR. J. PHARMACOL.) (Netherlands) 24 APR 1998, 347/2-3 (367)
CODEN: EJPHA ISSN: 0014-2999
PUBLISHER ITEM IDENTIFIER: S0014299998002222
DOCUMENT TYPE: Journal; Erratum
LANGUAGE: ENGLISH

5/3,AB/47 (Item 5 from file: 72)
DIALOG(R)File 72:EMBASE
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06717047 EMBASE No: 1996190188

Treatment with **antisense** oligodeoxynucleotide to the **GABA**(A) receptor gammainf 2 subunit increases convulsive threshold for beta-CCM, a benzodiazepine 'inverse agonist', in rats

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European Journal of Pharmacology (EUR. J. PHARMACOL.) (Netherlands) 1996, 306/1-3 (61-66)
CODEN: EJPHA ISSN: 0014-2999
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The gammainf 2 subunit of the gamma-aminobutyric acid type-A (**GABA**(A)) receptor is associated with the actions of benzodiazepines and related drugs. A phosphorothioate-modified **antisense** oligodeoxynucleotide directed against the gammainf 2 subunit was given by i.c.v. injection (18 mug in 2 mul saline) to male Sprague-Dawley rats every 12 h for 3 days. Controls received the corresponding sense oligodeoxynucleotide. 4-6 h after the last i.c.v. **treatment**, rats were given methyl-beta-carboline-3-carboxylate (beta-CCM), a benzodiazepine 'inverse agonist', by slow i.v. infusion. Compared to naive rats, the beta-GCM threshold dose was not affected by the sense oligodeoxynucleotide, but was increased 87% in **antisense** oligodeoxynucleotide-**treated** rats. The **treatment** had no effect on the seizure threshold for picrotoxin. Both **antisense** and sense oligodeoxynucleotide **treatments** slightly increased the threshold for strychnine seizures. The results suggest that **antisense** oligodeoxynucleotide **treatment** altered **GABA**(A) receptor composition and interfered with the actions of a benzodiazepine receptor ligand in vivo, and may provide a tool for studying regulation of receptor structure and function.

5/3,AB/48 (Item 6 from file: 72)
DIALOG(R)File 72:EMBASE

06566691 EMBASE No: 1996228053

alpha6 and gamma2 subunit **antisense** oligodeoxynucleotides alter gamma- aminobutyric acid receptor pharmacology in cerebellar granule neurons

Wei Jian Zhu; Jian Feng Wang; Vicini S.; Grayson D.R.
Department of Psychiatry, Medical College of Pennsylvania, Hahnemann University, 320 East North Avenue,Pittsburgh, PA 15210 United States

Molecular Pharmacology (MOL. PHARMACOL.) (United States) 1996, 50/1 (23-33)
CODEN: MOPMA ISSN: 0026-895X
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

To characterize the role of the alpha6 subunit in gamma-aminobutyric acid (**GABA**) receptors in cerebellar granule cells, primary cerebellar cultures were **treated** with **antisense** oligodeoxynucleotides (ODNs) complementary to and overlapping the initial codon of the alpha6 subunit cDNA. The specific reduction in the expression of the alpha6 receptor subunit protein after a 48-hr **antisense** ODN **treatment** was assessed with the use of immunoblot assays. Sister cultures were **treated** in parallel with mismatched (scrambled) ODNs. Inhibition of **GABA**-gated currents by furosemide, a selective inhibitor of **GABA**(A) receptors containing alpha6 subunits, was attenuated after the alpha6 **antisense treatment**. Furosemide was tested in parallel in transfected cells expressing various combinations of the alpha1 and alpha6 subunits, which showed that the relative abundance of these subunit mRNAs determines the extent of furosemide-induced inhibition of **GABA**-gated currents. Compared with control or mismatched ODN-**treated** cell cultures, **treatment** of granule neurons with alpha6

antisense ODNs caused a decrease in **GABA**-induced maximal current density and increased the half-maximal concentration derived from **GABA** dose-response curves. Furthermore, the depletion of alpha6 subunits from cerebellar granule cells enhanced flunitrazepam-induced potentiation of **GABA**-activated currents. In contrast, gamma2 **antisense** ODN **treatments** of cell cultures increased the receptor sensitivity to **GABA** and potently decreased the response to flunitrazepam. Our results show that alpha6 and gamma2 subunit expression can be blocked with the use of synthetic ODNs and that these subunits are crucial determinants of the pharmacological properties of native **GABA** (A) receptors in cerebellar granule cells.

5/3,AB/49 (Item 7 from file: 72)
DIALOG(R)File 72:EMBASE

06125346 EMBASE No: 1995156230
Antisense oligonucleotide-induced block of individual **GABA**(A) receptor a subunits in cultured visual cortex slices reduces amplitude of evoked inhibitory postsynaptic currents
Brussaard A.B.; Baker R.E.
Graduate School Neurosciences, Research Institute Neuroscience, Vrije Universiteit, De Boelelaan 1087,1081 HV Amsterdam Netherlands
Neuroscience Letters (NEUROSCI. LETT.) (Ireland) 1995, 191/1-2 (111-115)
CODEN: NELED ISSN: 0304-3940
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Whole cell patch clamp recordings were made in layer II-IV from organotypic slices of rat primary visual cortex, explanted at postnatal day 6 and maintained in a serum-free medium. Neurons evinced current clamp characteristics typical for stellate cells. Between 7 and 21 days in culture, both glutamate- and **GABA**-mediated postsynaptic currents were observed. Long-term culturing in the presence of a degenerate 15-mer **antisense** oligonucleotide directed against the transcripts of all a subunits genes of the **GABA**(A) receptor resulted in a dose dependent reduction of evoked **GABA** synaptic currents. This reduction was maximal (80%) at 20 muM. A randomized control oligo had no effect. Evoked glutamatergic excitatory postsynaptic currents were unaffected following oligo **treatment**. A 15-mer **antisense** oligo directed against the alpha1 subunit gave variable effects: in some cells the amplitude of evoked GABAergic inhibitory postsynaptic currents (IPSCs)) was-reduced by 50-75%, while in other cells recorded from the same slices, there was little or no effect. An **antisense** oligo, directed against the alpha2 subunit, however, gave a consistent and robust 80% reduction of the amplitude of evoked IPSCs. A 15-mer 3-base mismatch oligo against alpha2 had no effect. We conclude that the alpha2 subunit functions in postsynaptic **GABA**(A) receptors located on or close to the cell bodies of stellate cells. The role of the alpha1 subunit is less clear, but this subunit seems spatially differentiated. The in situ **antisense** oligo technique should provide further insight into the biophysical and pharmacological consequences of the subunit composition of ligand gated channels at functional synapses.

5/3,AB/50 (Item 8 from file: 72)
DIALOG(R)File 72:EMBASE

05639369 EMBASE No: 1994045119
Intracerebral administration of **antisense** oligodeoxynucleotides to GADinf 6$D5 and GADinf 6inf 7 mRNAs modulate reproductive behavior in the female rat
McCarthy M.M.; Masters D.B.; Rimvall K.; Schwartz-Giblin S.; Pfaff D.W.

Department of [redacted]ysiology, University of Maryland School of Medicine, 655 West Baltimore Street,Baltimore, MD 20201-1559 [redacted]nited States
Brain Research (BRAIN RES.) (Netherlands) 1994, 636/2 (209-220)
CODEN: BRREA ISSN: 0006-8993
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Increased **GABA** activity in the medial hypothalamus (HYP) and midbrain central gray (MCG), but not the preoptic area (POA), facilitates sexual receptivity in the female rat. In the current experiments, ovariectomized females were chronically **treated** with estrogen (via silastic capsules) to maintain a continuously high level of lordosis response. Administration of crystalline **antisense** oligodeoxynucleotide to the **GABA** synthetic enzyme, GADinf 6inf 7, into the HYP and MCG significantly and reversibly reduced lordosis response for 1-2 days, but did not inhibit lordosis when administered into the POA. Administration of a control oligonucleotide, consisting of the same nucleotide bases but in a scrambled sequence, did not significantly modulate behavior when infused into any brain areas. When oligodeoxynucleotide **antisense** to GADinf 6inf 7 was suspended in oil and then infused into the HYP or MCG it was more effective and resulted in less inter-animal variability. Subsequent experiments involving infusions into the MCG compared the effectiveness of **antisense** oligonucleotides to the two different forms of **GAD**, known as GADinf 6$D5 and GADinf 6inf 7. Oligodeoxynucleotides **antisense** to the mRNA for either gene were effective at reducing lordosis behavior but with a different time course. Oligonucleotide **antisense** to GADinf 6inf 7 significantly reduced behavior within 24 h of infusion and there was full recovery by 4 days post-infusion. GADinf 6$D5 **antisense** oligonucleotide did not significantly reduce behavior until 48 h post infusion and animals did not fully recover to pretest levels of lordosis until 5 days post-infusion. When **antisense** oligonucleotide for the two genes was administered simultaneously, the inhibition of lordosis was maximal at 24 h and stayed depressed for 4 days. There did not appear to be an additive effect of the two different **antisense** oligonucleotides when administered together. Tissue **GABA** levels in HYP and MCG of individual rats assayed by HPLC were no longer correlated with lordosis score after **antisense** oligonucleotide infusion but were after infusions of scrambled control oligos. Immunoblotting for the two forms of **GAD** revealed that GADinf 6inf 7 **antisense** oligonucleotide infusion led to significant decreases in both GADinf 6inf 7 and GADinf 6$D5 protein levels as compared to infusions of scrambled control oligo. In addition, the levels of a neuronal marker, neuron-specific enolase, also decreased (although nonsignificantly) suggesting either a temporary shutdown of protein synthesis or a degeneration of GABAergic neurons after GADinf 6inf 7 **antisense** oligonucleotide infusion.

5/3,AB/51 (Item 9 from file: 72)
DIALOG(R)File 72:EMBASE

05541147 EMBASE No: 1993309247
A specific **antisense** oligodeoxynucleotide to mRNAs encoding receptors with seven transmembrane spanning regions decreases muscarinic minf 2 and gamma-aminobutyric acid(B) receptors in rat cerebellar granule cells
Holopainen I.; Wojcik W.J.
Medical-Dental Bldg., Georgetown University, 3900 Reservoir Rd. N.W.,Washington, DC 20007 United States
Journal of Pharmacology and Experimental Therapeutics (J. PHARMACOL. EXP. THER.) (United States) 1993, 264/1 (423-430)
CODEN: JPETA ISSN: 0022-3565
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Many receptors that inhibit adenylyl cyclase belong to a common superfamily of receptors that couple to guanine nucleotide binding proteins. These receptors are thought to span the membrane seven times and to have a highly homologous amino acid sequence (LACADL) in the second membrane spanning region. The **antisense** oligodeoxynucleotide seven-transmembrane spanning receptor (7TMR), a 15-mer that binds to mRNA encoding this amino acid sequence, was added to cerebellar granule neuron cultures to decrease receptors of this superfamily. Intact **antisense** 7TMR was found to enter neurons. This 4- to 6-day **treatment** with **antisense** oligonucleotide decreased the total number of muscarinic receptor binding sites by about 40% and completely eliminated muscarinic minf 2 receptors that inhibit cyclic AMP formation. **Antisense** 7TMR **treatment** at 25 muM prevented the gamma-aminobutyric acid (**GABA**)(B)- mediated inhibition of cyclic AMP formation by about 40%. The **treatment** was effective in decreasing **GABA**(A) receptors only when the **antisense** oligonucleotide was given 1 day after plating the cells, and the receptor response assay was performed 6 days later. The half-maximal concentration of **antisense** 7TMR was approximately 5 muM in blocking **GABA**(B) receptors. **Antisense** 7TMR appeared to be specific because another **antisense** oligodeoxynucleotide sequence (15-mer) having four mismatches with 7TMR had no effect on either muscarinic minf 2 or **GABA**(B) receptor-mediated responses and did not affect the total number of muscarinic binding sites. These results are consistent with the view that **antisense** oligonucleotides decrease proteins in which the nucleotide sequence is known such as the muscarinic minf 2 receptor. These data also suggest that the **GABA**(B) receptor which inhibits cyclic AMP formation might belong to the superfamily of receptors having seven-transmembrane spanning regions.

00103547
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Increased Concentrations of Presynaptic Proteins in the Cingulate Cortex of Subjects With Schizophrenia (ARTICLE)

GABRIEL, STEVEN M.; HAROUTUNIAN, VAHRAM; POWCHIK, PETER; HONER, WILLIAM G.; DAVIDSON, MICHAEL; DAVIES, PETER; DAVIS, KENNETH L.
Archives of General Psychiatry
June, 1997; Original Article: tzy559
LINE COUNT: 00669

Background: Cytoarchitectural and neurochemical studies demonstrate disorganization in the cerebral cortex in schizophrenia, which perhaps underlies the severe behavioral disturbances of the disease. This neuronal disarray should be accompanied by synaptic abnormalities. As such, presynaptic proteins have proved valuable indexes of synaptic density and their concentrations have correlated markedly with synaptic loss. Our study sought to determine whether abnormalities exist in the concentrations of presynaptic proteins in the postmortem cerebral cortex of subjects with schizophrenia. Methods: Presynaptic protein immunoreactivities were assessed in 4 different cerebrocortical regions derived from 16 elderly controls, 19 elderly subjects with schizophrenia, and 24 subjects with Alzheimer's disease. Tissues were assayed with the monoclonal antibodies EP10 and SP4, which recognize synaptophysin, and the monoclonal antibodies SP6 and SP14, which detect syntaxin and synaptosomal-associated protein-25-kd immunoreactivities, respectively. Results: In subjects with schizophrenia relative to controls, presynaptic proteins were increased in the cingulate cortex, but wereunchanged in the temporal, frontal, and parietal cortices. In contrast, when cases with Alzheimer's disease were

compared with controls, presynaptic proteins were decreased in the frontal, temporal, and parietal samples. Conclusions: These findings reveal changes in the synaptic organization of the cingulate cortex in schizophrenia relative to other areas examined. These changes are distinct from the deficits inpresynaptic proteins observed in Alzheimer's disease. Arch Gen Psychiatry. 1997;54:559-566

5/3,AB/53 (Item 2 from file: 442)
DIALOG(R)File 442:AMA Journals

00098580

Catching up on Schizophrenia The Fifth International Congress on Schizophrenia Research, Warm Springs, Va, April 8-12, 1995 (ARTICLE)

BUCKLEY, PETER F.; BUCHANAN, ROBERT W.; TAMMINGA, CAROL A.
Archives of General Psychiatry
May, 1996; News and Views: tzy456
LINE COUNT: 00592

It is axiomatic that the diversity and ingenuity of strategies in thestudy of schizophrenia bear testimony to the complexity of this disorder. Accordingly, the opportunity for investigators of diverse interests to share their latest findings and be informed of developments in key areas of science is critical to advance our understanding of schizophrenia. Nearly 700 investigators from around the world gathered at Warm Springs, Va, to present their data at the Fifth International Congress on Schizophrenia Research (April 8-12, 1995). This 5-day conference, held every other year alternating with the European Winter Workshop on Schizophrenia, is co-organized by S. Charles Schulz, MD, Case Western Reserve University, Cleveland, Ohio,and Carol Tamminga, MD, Maryland Psychiatric Research Center, University of Maryland at Baltimore. Drs Schulz and Tamminga first held the Congress in 1987 in Clearwater, Fla, with 170 investigators presenting. The Congress has flourished since then and is now the largest research meeting devoted solely to schizophrenia. The Congress organizers, the program coordinator (Jeffrey Lieberman, MD, Hillside Hospital, Glen Oaks, NY), and the Congress coordinator (Susan Nusbaum, Maryland Psychiatric Research Center) are congratulated on the success of this event and its contribution to fostering initiatives and collaborations within schizophrenia research.

5/3,AB/54 (Item 3 from file: 442)
DIALOG(R)File 442:AMA Journals

00094283

Gene Expression for Glutamic Acid Decarboxylase Is Reduced Without Loss of Neurons in Prefrontal Cortex of Schizophrenics (ARTICLE)

AKBARIAN, SCHAHRAM; KIM, JAMES J.; POTKIN, STEVEN G.; HAGMAN, JENNIFER O.
; TAFAZZOLI, ALIREZA; BUNNEY, WILLIAM E.; JONES, EDWARD G.
Archives of General Psychiatry
Apr, 1995; Original Article: ps_258
LINE COUNT: 00720

Background: Up-regulation of y-aminobutyric acidA/ (GABAA/) receptorsand decreased **GABA** uptake in the cerebral cortex of schizophrenics suggest altered GABAergic transmission, which could be caused by primary disturbance of **GABA** synapses or by decreased production of the

transmitter. D[redacted]eased production could be due t[redacted]a shutdown in **GABA** production or [redacted] loss of **GABA** neurons caused b[redacted]ell death or their failure to migrate to the cortex during brain development. Methods: To discriminate between these possibilities, we quantifiedlevels of messenger RNA (mRNA) for the 67-kd isoform of glutamic aciddecarboxylase (**GAD**), the key enzyme in **GABA** synthesis, and the numberand laminar distribution of **GAD** mRNA-expressing neurons in the dorsolateral prefrontal cortex (DLPFC) of schizophrenics and matched controls, using in situ hybridization-histochemistry, densitometry, and cell-counting methods. These data were compared with the total number of neurons, the number of small, round or ovoid neurons 8 to 15 um in diameter, and overall frontal lobe volume. As a control, mRNA levels for type II calcium-calmodulin-dependent protein kinase (CamIIK) were quantified. Results: Schizophrenics showed a pronounced decrease in **GAD** mRNA levels in neurons of layer I (40%) and layer II (48%) and an overall 30% decrease in layers III to VI. There were also strong overall reductions in **GAD** mRNA levels. The CamIIK mRNA levels showed no significant differences between samples. No differences were found inthe total number of neurons nor in small, round or ovoid neurons, which should include a majority of the **GABA** cells. Prefrontal gray and white matter volume did not differ significantly between controlsand schizophrenics. Conclusions: The prefrontal cortex of schizophrenics shows reduced expression for **GAD** in the absence of significant cell loss. This may be brought about by an activity-dependent down-regulation associated with the functional hypoactivity of the DLPFC. The lack of significant alterations in cell numbers in the DLPFC and frontal lobevolume in schizophrenics also implies that overall cortical neuronal migration had not been compromised in development. Previous reports of altered neuronal distribution in the subcortical white matter of schizophrenic brains in comparison with that of controls may indicatedisturbances of migration or programmed cell death in the cortical subplate, leading to altered connection formation in the overlying cortex of schizophrenics and activity-dependent down-regulation of neurotransmitter-related gene expression. (Arch Gen Psychiatry. 1995;52:258-266)

5/3,AB/55 (Item 4 from file: 442)
DIALOG(R)File 442:AMA Journals

00087670

A Primer of Current Molecular Genetic Strategies for Clinicians (ARTICLE)

HOOPER, PLEASANT F.
Archives of Otolaryngology
oct, 1993; State of the Art: p1085
LINE COUNT: 01019

For the clinician to take full advantage of the rapid advances in molecular medicine, a working knowledge of the recombinant DNA methodologies employed will be required. This primer introduces current cloning strategies by examination of the cloning of the cystic fibrosis gene, an opioid receptor, and olfactory receptors that used the methodologies of DNA linkage analysis, functional cloning, and polymerase chain reaction with degenerate oligonucleotide primers, respectively. Molecular information obtainedafter cloning has had immediate effects on diagnosis and genetic counseling and holds the promise of novel **treatment** strategies, including somatic gene therapy. (Arch Otolaryngol Head Neck Surg. 1993;119:1085-1094)
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74150 GABA
6498 GAD

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            1172  GAD65
             725  GAD67
            1218  GLUTAMIC ACID DECARBOXYLASE
           74725  PARKINSON?
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            2973  TRIPLEX
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 8/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2000 Dialog Corporation. All rts. reserv.

09823500   99079264
  Functional neuroanatomy of the basal ganglia as studied by dual-probe
microdialysis.
  O'Connor WT
  Department of Human Anatomy and Physiology, University College, Dublin,
Ireland. woconn@iveagh.ucd.ie
  Nuclear medicine and biology (ENGLAND)  Nov 1998,  25 (8) p743-6,  ISSN
0969-8051  Journal Code: BOO
  Languages: ENGLISH
  Document type: JOURNAL ARTICLE
  Dual probe microdialysis was employed in intact rat brain to investigate
the effect of intrastriatal perfusion with selective dopamine D1 and D2
receptor agonists and with c-fos antisense oligonucleotide on (a)
local GABA release in the striatum; (b) the internal segment of the
globus pallidus and the substantia nigra pars reticulata, which is the
output site of the strionigral GABA pathway; and (c) the external
segment of the globus pallidus, which is the output site of the
striopallidal GABA pathway. The data provide functional in vivo
evidence for a selective dopamine D1 receptor-mediated activation of the
direct strionigral GABA pathway and a selective dopamine D2 receptor
inhibition of the indirect striopallidal GABA pathway and provides a
neuronal substrate for parallel processing in the basal ganglia regulation
of motor function. Taken together, these findings offer new therapeutic
strategies for the treatment of dopamine-linked disorders such as
Parkinson's disease, Huntington's disease, and schizophrenia.


 8/3,AB/2     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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11884543   BIOSIS NO.: 199900130652
Kir6.2 oligoantisense administered into the globus pallidus reduces
  apomorphine-induced turning in 6-OHDA hemiparkinsonian rats.
AUTHOR: Lamensdorf Itschak(a); Meiri Noam; Harvey-White Judith; Jacobowitz
  David M; Kopin Irwin J
AUTHOR ADDRESS: (a)Natl. Inst. Neurol. Dis. Stroke, Clin. Neurosci. Branch,
  Build. 10, Room 4D-20, Natl. Inst. Heal**USA
JOURNAL: Brain Research  818 (2):p275-284 Feb. 13, 1999
ISSN: 0006-8993
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DOCUMENT TYPE: [redacted]icle
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: ATP-sensitive inwardly rectifying potassium channels (KATPs) couple cell metabolism with its membrane potential. The best characterized KATP is the pancreatic KATP which is an heteromultimer of Kir6.2 and SUR1 protein subunits. KATPs are found in a variety of excitable cells, including neurons of the central nervous system. Basal ganglia (BG), especially in the substantia nigra (SN) reticulata and the globus pallidus (GP), have a high density of KATPs. Pharmacological modulation of the KATPs within the BG alters GABAergic activity and produces behavioural changes. However, the relatively high concentrations of drugs used might not have been entirely selective for the KATPs and may have acted at presynaptic nerve terminals as well as on the post-synaptic neurons. As an alternative means of examining the role of KATPs in regulating motor behavior, we used oligoantisense technology to diminish selectively Kir6.2 formation in the GP neurons. We then examined the effect of reduction in Kir6.2 expression on apomorphine-induced turning behavior in rats with unilateral 6-hydroxydopamine (6-OHDA) lesions of the SN. Two weeks after injection of 6-OHDA, contralateral circling in response to apomorphine (0.25 mg/kg sc) was recorded. Kir6.2 **antisense** oligodeoxyribonucleotide (ODN) was then administered daily for 6 days into the GP ipsilateral to the 6-OHDA injection. Responses to apomorphine were then tested again and the animals killed to determine the effect of the **antisense** ODN on Kir6.2 mRNA. Administration of Kir6.2 **antisense** ODN significantly attenuated apomorphine-induced contralateral turning and specifically reduced Kir6.2 mRNA in the injected GP. These results are consistent with pharmacological experiments which suggest that KATP channels in the GP are involved in motor responses to apomorphine in 6-OHDA lesioned rats, localizing the effects to the GP neurons, probably through modulation of the GABAergic system.

8/3,AB/3 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE

10514669 EMBASE No: 1999425955
Enigma of the peripheral benzodiazepine receptor
Gavish M.; Bachman I.; Shoukrun R.; Katz Y.; Veenman L.; Weisinger G.; Weizman A.
Dr. M. Gavish, Department of Pharmacology, Bruce Rappaport Faculty of Medicine, Technion-Israel Inst. of Technology, P.O.B. 9649, 31096 Haifa Israel
AUTHOR EMAIL: mgavish@x.technion.ac.il
Pharmacological Reviews (PHARMACOL. REV.) (United States) 1999, 51/4 (629-650)
CODEN: PAREA ISSN: 0031-6997
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 249

The combined facts that the PBR gene is conserved throughout evolution from bacteria to humans and that this gene appears to have the hallmarks of a typical housekeeping gene suggest that this gene's product has a basic cellular function. Even though many functions have been attributed to this gene product, its primary roles remain an open question. Hence, a resolution of the primary functions of the PBR gene products must be a central theme for future work with PBRs. One of the often-suggested putative roles attributed to PBRs is as the rate-limiting step in steroidogenesis. The relevance of PBRs for steroidogenesis is reflected by their abundance in the adrenal gland and in male and female gonadal tissues. It is explained that this role is mediated through regulation of

cholesterol transport from the cytoplasm to the mitochondrial matrix. Because another protein, StAR, has the same attribute, either a biochemical redundancy is apparent or some interaction between these proteins may mediate mitochondrial cholesterol transport. Another putative function for PBRs involves a regulatory role in cell proliferation. This role may be closely associated with some type of regulatory function in cellular respiration, which also is one of the many assigned roles for the PBR gene product. Hence, it has been argued that the dysregulation of PBRs in some tissues may lead to diseases of cellular proliferation, including cancer. A number of reports have, in fact, found PBR overexpression in particular tumor types and some transformed cell lines. In all of these cases, a causative pathology for PBR overexpression has never been shown, hence not ruling out a passive coincident dysregulation of the expression of PBR genes in these tumors. In support of this, we recently reported that on **antisense** knockout of PBRs in a mouse Leydig tumor cell line, no apparent changes in the cell proliferation or cell cycle were measurable (Kelly-Hershkovitz et al., 1998). We acknowledge that this may be unique to these specific cells, and hence a more extensive study must still be undertaken. Furthermore, other as-yet-undefined effects of PBR overexpression may be important in malignancy. In this respect, the modulatory role of PBRs on immune system function should also be taken into consideration. In addition, at behavioral levels, PBRs appear to be involved in the biological coping with stress and anxiety disorders. It has been suggested that PBRs play a role in the regulation of several stress systems such as the HPA axis, the sympathetic nervous system, the renin-angiotensin axis, and the neuroendocrine-immune axis. In these systems, acute stress typically leads to increases in PBR density, whereas chronic stress typically leads to decreases in PBR density. Furthermore, in **GAD**, PD, GSP, and PTSD, PBR density is typically decreased in platelets. In the brain, where PBRs are associated with glial cells, PBRs are increased in specific brain areas in neurodegenerative disorders and also after neurotoxic and traumatic-ischemic brain damage. These accumulating data indicate a possible role for PBR in adaptation of the organism to stress and brain damage. Because PBRs appear to be involved in a large variety of physical diseases, mental disorders, and responses to stress, clinical benefit may be attainable by the increasing pharmacological knowledge surrounding these receptors. Nevertheless, there still is much to be learned about the structure of PBRs as well as their cellular location, regulation of gene expression of the PBR subunits, and the interaction between PBR subunits. As mentioned above, other proteins like StAR may also be involved in this complex. A molecular understanding of the protein component subunits, as well as how they fit together and function as a whole, still requires much work. The 18-kDa isoquinoline-binding PBR subunit is not only found on the mitochondrial membrane; it is also found to a lesser extent on the plasma membrane of the cell, as well as on the membrane of other cellular organelles. Its role, structure, and other interacting subunits in these other cellular locations also must be addressed. Much has been learned in the decade since the 18-kDa PBR subunit mRNA was cloned and still much must be learned from and about the genes encoding PBR subunits. This will involve many levels of study. It may be that once we understand why evolution so carefully preserves the sequence of the 18-kDa PBR subunit gene, we will be able to uncover new biochemical pathways that will link the various putative PBR functions now being discussed. Only the future can tell.

00087670

A Primer of Current Molecular Genetic Strategies for Clinicians (ARTICLE)

HOOPER, PLEAS[redacted] F.
Archives of Otolaryngology
oct, 1993; State of the Art: p1085
LINE COUNT: 01019

For the clinician to take full advantage of the rapid advances in molecular medicine, a working knowledge of the recombinant DNA methodologies employed will be required. This primer introduces current cloning strategies by examination of the cloning of the cystic fibrosis gene, an opioid receptor, and olfactory receptors that used the methodologies of DNA linkage analysis, functional cloning, and polymerase chain reaction with degenerate oligonucleotide primers, respectively. Molecular information obtainedafter cloning has had immediate effects on diagnosis and genetic counseling and holds the promise of novel treatment strategies, including somatic gene therapy. (Arch Otolaryngol Head Neck Surg. 1993;119:1085-1094)

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            267  S9
        3541775  TREAT?
    S10     127  S9 AND TREAT?
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in RD set
...examined 50 records  (100)
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 11/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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10519140 20359597

Microstimulation-induced **inhibition** of neuronal firing in human globus pallidus.

Dostrovsky JO; Levy R; Wu JP; Hutchison WD; Tasker RR; Lozano AM
Department of Physiology, University of Toronto, Toronto, Ontario M5S 1A8, Canada. j.dostrovsky@utoronto.ca

Journal of neurophysiology (UNITED STATES) Jul 2000, 84 (1) p570-4, ISSN 0022-3077 Journal Code: JC7
Contract/Grant No.: NS-36824, NS, NINDS
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Neurosurgical **treatment** of **Parkinson** 's disease (PD) frequently employs chronic high-frequency deep brain stimulation (DBS) within the internal segment of globus pallidus (GPi) and can very effectively reduce L-dopa-induced dyskinesias and bradykinesia, but the mechanisms are unknown. The present study examined the effects of microstimulation in GPi on the activity of neurons close to the stimulation site. Recordings were made from GPi using two fixed or independently controlled microelectrodes, with the electrode tips usually approximately 250 or >600 micrometer apart in PD patients undergoing stereotactic exploration to localize the optimal site for placement of a lesion or DBS electrode. The spontaneous activity of nearly all of the cells (22/23) recorded in GPi in three patients was **inhibited** by microstimulation at currents typically <10 microA (0.15-ms pulses at 5 Hz). The **inhibition** had a duration of 10-25 ms at threshold. These findings suggest that microstimulation within GPi preferentially excites the axon

terminals of [redacted]iatal and/or external pallida[redacted]eurons causing release of **GABA** and **inhibition** of GPi neurons.

11/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10499693 20362972
Chronic supranigral infusion of BDNF in normal and MPTP-**treated** common marmosets.
Pearce RK; Costa S; Jenner P; Marsden CD
Neurodegenerative Diseases Research Centre, Biomedical Sciences Division, King's College London, and The National Hospital for Neurology, United Kingdom.
Journal of neural transmission (AUSTRIA) 1999, 106 (7-8) p663-83, Journal Code: CIJ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
BDNF or vehicle were administered by unilateral supranigral infusion in normal and chronically lesioned MPTP-**treated** common marmosets (Callithrix jacchus) for four weeks and locomotor activity, disability and response to apomorphine were assessed with nigral TH, GFAP and **GAD** immunoreactivity and striatal [3H]mazindol autoradiography. Selective contraversive orientation and ipsilateral neglect evolved in MPTP-**treated** marmosets receiving BDNF with no significant difference in disability or locomotor activity when compared to the vehicle-infused group. Apomorphine produced an ipsiversive rotational bias in BDNF-**treated** animals. In normal animals infused with BDNF contralateral neglect, ipsiversive turning, postural instability and ataxia rapidly evolved. In MPTP-**treated** marmosets BDNF caused increased ipsilateral striatal [3H]mazindol binding with increased somatic size and staining intensity in **GAD** -immunoreactive cells and a 10-20% loss of nigral TH-immunoreactive cells with increased GFAP staining. In normal common marmosets, both vehicle and BDNF infusion decreased nigral TH-immunoreactivity. Chronic supranigral infusion of BDNF alters motor behaviour and spatial attention in MPTP-**treated** marmosets which may reflect altered function in residual nigral dopaminergic neurons and brainstem GABAergic neurons and in normal animals produces behavioural and histological signs of nigrostriatal hypofunction.

11/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10416806 20249089
125I-CGP, 64213 binding to **GABA** (B) receptors in the brain of monkeys: effect of MPTP and dopaminomimetic **treatments**.
Calon F; Morissette M; Goulet M; Grondin R; Blanchet PJ; Bedard PJ; Di Paolo T
Oncology and Molecular Endocrinology Research Center, Laval University Medical Center (CHUL), Quebec, Qc, G1V 4G2, Canada.
Experimental neurology (UNITED STATES) May 2000, 163 (1) p191-9, ISSN 0014-4886 Journal Code: EQF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Much evidence indicates that abnormal **GABA** neurotransmission may be implicated in the pathophysiology of **Parkinson**'s disease (PD) and dopaminomimetic-induced dyskinesias (DID). In this study, autoradiography using (125)I-CGP 64213 was performed to investigate **GABA**(B) receptor density in the brain of control monkeys as well as monkeys with MPTP-induced nigrostriatal depletion. Three MPTP monkeys received pulsatile administrations of the D1 dopamine (DA) receptor agonist (SKF 82958) whereas a long-acting D2 DA receptor agonist (cabergoline) was given to

another thr[redacted] animals. SKF 82958 [redacted]**eatment** relieved **parkinsonian** symptoms but two of three animals developed DID. Cabergoline induced a comparable motor benefit effect without persistent DID. (125)I-CGP 64213 binding to **GABA**(B) receptors was heterogeneous throughout the brain with the highest levels in the medial habenula of the thalamus. MPTP induced a decrease (-40%) of (125)I-CGP 64213 binding to **GABA**(B) receptors in the substantia nigra pars compacta (SNpc) and an increase (+29%) in the internal segment of the globus pallidus (GPi). This increase in the GPi was not affected by SKF 82958 but partly reversed by cabergoline. No change was seen in the striatum, the thalamus, the external segment of the globus pallidus, and the substantia nigra pars reticulata following MPTP and dopaminomimetic **treatments**. The changes of **GABA** (B) receptors observed in the SNpc and in the GPi suggest that alteration of **GABA** (B) receptors may play a role in the pathophysiology of PD and DID. Copyright 2000 Academic Press.

11/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10365952 20222788
Molecular basis of levodopa-induced dyskinesias.
Calon F; Grondin R; Morissette M; Goulet M; Blanchet PJ; Di Paolo T; Bedard PJ
Centre de Recherches en Endocrinologie Moleculaire, Le Centre Hospitalier Universitaire de Quebec, and Faculty of Pharmacy, Laval University, Quebec, Canada.
Annals of neurology (UNITED STATES) Apr 2000, 47 (4 Suppl 1) pS70-8, ISSN 0364-5134 Journal Code: 6AE
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
A series of experiments were performed in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of **parkinsonism** for the purpose of understanding the mechanism of dopaminergic dyskinesias. Dyskinesias can be induced in this model by de novo **treatment** with levodopa, or selective D1 or D2 agonists, provided the drugs are short acting and administered in the pulsatile mode. Biochemical analysis of the brains revealed several alterations in dopamine receptor-binding and messenger RNA message following denervation and dopaminergic **treatment** , but none that clearly correlated with the presence of dyskinesias. On the other hand, gamma-aminobutyric acid (**GABA**)A binding was increased in the internal segment of the globus pallidus of dyskinetic MPTP monkeys. This was observed consistently and could be associated with an exaggerated response to GABAergic **inhibitory** inputs in this strategic structure. Increased preproenkephalin message was also found to correlate with dyskinesias and may be linked to changes in **GABA** receptors. **Treatments** that caused dyskinesias induced, in the striatum, chronic Fos proteins of the deltaFosB family which, when coupled with Jun-D, form AP-1 complexes that can affect several genes, including enkephalin and N-methyl-D-aspartate receptor. We suggest that levodopa-induced dyskinesias represent a form of pathological learning, which results from deficient gating of glutamatergic inputs to the striatum by dopamine.

11/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10346638 20199885
Role for dopamine in malonate-induced damage in vivo in striatum and in vitro in mesencephalic cultures.
Moy LY; Zeevalk GD; Sonsalla PK
Department of Neurology, University of Medicine and Dentistry of New

Jersey, Robert [redacted]d Johnson Medical School, Pisc[redacted]way, USA.
Journal of neurochemistry (UNITED STATES) Ap[redacted]2000, 74 (4) p1656-65, ISSN 0022-3042 Journal Code: JAV
Contract/Grant No.: AG08479, AG, NIA; MH12390, MH, NIMH; NS36157, NS, NINDS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Defects in mitochondrial energy metabolism have been implicated in the pathology of several neurodegenerative disorders. In addition, the reactive metabolites generated from the metabolism and oxidation of the neurotransmitter dopamine (DA) are thought to contribute to the damage to neurons of the basal ganglia. We have previously demonstrated that infusions of the metabolic **inhibitor** malonate into the striata of mice or rats produce degeneration of DA nerve terminals. In the present studies, we demonstrate that an intrastriatal infusion of malonate induces a substantial increase in DA efflux in awake, behaving mice as measured by in vivo microdialysis. Furthermore, pretreatment of mice with tetrabenazine (TBZ) or the TBZ analogue Ro 4-1284 (Ro-4), compounds that reversibly **inhibit** the vesicular storage of DA, attenuates the malonate-induced DA efflux as well as the damage to DA nerve terminals. Consistent with these findings, the damage to both DA and **GABA** neurons in mesencephalic cultures by malonate exposure was attenuated by pretreatment with TBZ or Ro-4. **Treatment** with these compounds did not affect the formation of free radicals or the **inhibition** of oxidative phosphorylation resulting from malonate exposure alone. Our data suggest that DA plays an important role in the neurotoxicity produced by malonate. These findings provide direct evidence that **inhibition** of succinate dehydrogenase causes an increase in extracellular DA levels and indicate that bioenergetic defects may contribute to the pathogenesis of chronic neurodegenerative diseases through a mechanism involving DA.

11/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10305564 20148310
Noradrenoceptor antagonism with idazoxan improves L-dopa-induced dyskinesias in MPTP monkeys.
Grondin R; Tahar AH; Doan VD; Ladure P; Bedard PJ
Department of Medicine, Faculty of Medicine, Laval University Research Center, Ste-Foy, Quebec, Canada.
Naunyn-Schmiedeberg's archives of pharmacology (GERMANY) Feb 2000, 361 (2) p181-6, ISSN 0028-1298 Journal Code: NTQ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Treatment of **Parkinson**'s disease with L-dopa is plagued in a majority of patients by dyskinesias. Noradrenaline/dopamine interactions are proposed on behavioral, biochemical, physiological and anatomical grounds. The aim of the study was to test the potential antidyskinetic effect of the alpha2-adrenoceptor antagonist, idazoxan, in a primate model of **Parkinson** 's disease. Six female cynomolgus monkeys previously rendered **parkinsonian** by the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahyd ropyridine (MPTP) and presenting an unchanged syndrome for several months were used. All responded readily to L-dopa but had developed dyskinesias which were manifested with each dose. In the first part of the study, seven doses of idazoxan (ranging from 0.25 mg/kg to 10 mg/kg, p.o.) were administered together with the vehicle or in combination with a fixed dose of L-dopa/benserazide (100/25 mg, p.o.). In the second part of the study, a fixed dose of idazoxan (7.5 mg/kg) was administered daily for 10 days and L-dopa was added to idazoxan on days 1, 4, 7 and 10. Vehicle (empty capsule) was used as control. Idazoxan, by itself (ranging from 5 mg/kg to 10 mg/kg), increased locomotor activity and improved the disability score with virtually no dyskinesias in three animals. In combination with L-dopa, idazoxan did not impair the antiparkinsonian response but significantly

reduced dyskinesias in all six animals up to 65 [redacted] doses of 7.5 mg/kg and 10 mg/kg and delayed their onset, so that the "ON" state without dyskinesias was prolonged. The antidyskinetic effect of idazoxan was maintained when repeatedly administered for 10 days. On day 10, the locomotor response to L-dopa was significantly potentiated by chronic administration of idazoxan. Our results indicate that idazoxan has some antiparkinsonian effect of its own and may constitute a useful adjunct to L-dopa as it can reduce dyskinesias without impairing the relief of symptoms, this effect being maintained over time in this model.

11/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10274407 20114531
Inhibition of catechol-O-methyltransferase (COMT) in the brain does not affect the action of dopamine and levodopa: an in vitro electrophysiological evidence from rat mesencephalic dopamine neurons.
Mercuri NB; Federici M; Bernardi G
IRCCS Santa Lucia and Clinica Neurologica, Universita di Tor Vergata, Roma, Italy. Mercurin@med.uniroma2.it
Journal of neural transmission (AUSTRIA) 1999, 106 (11-12) p1135-40, Journal Code: CIJ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In order to study whether the membrane hyperpolarization and firing **inhibition** caused by dopamine and levodopa on rat midbrain dopamine cells are affected by the **inhibition** of brain catechol-O-methyl-transferase (COMT), intracellular electrophysiological recordings were made from these neurons maintained in vitro. Here we report that a **treatment** of the cerebral tissue with tolcapone, a central and peripheral **inhibitor** of COMT, does not change the membrane responses of midbrain dopamine neurons to dopamine and levodopa. The lack of modification of the dopaminergic effects by tolcapone suggests that the pharmacological **inhibition** of intracerebral COMT does not have detectable action on dopamine neurotransmission. Therefore, the therapeutic action of tolcapone in **Parkinson**'s disease, might be dependent on the reduction of COMT activity in the extracerebral tissue.

11/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10125895 99172144
Effect of repeated L-DOPA, bromocriptine, or lisuride administration on preproenkephalin-A and preproenkephalin-B mRNA levels in the striatum of the 6-hydroxydopamine-lesioned rat.
Henry B; Crossman AR; Brotchie JM
Division of Neuroscience, School of Biological Sciences, University of Manchester, 1.124 Stopford Building, Manchester, M13 9PT, United Kingdom.
Experimental neurology (UNITED STATES) Feb 1999, 155 (2) p204-20, ISSN 0014-4886 Journal Code: EQF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Abnormal involuntary movements, or dyskinesias, plague current symptomatic approaches to the **treatment** of **Parkinson**'s disease. The neural mechanisms underlying the generation of dyskinesia following repeated l-3,4-dihydroxyphenylalanine (L-DOPA) or dopamine agonist administration in **Parkinson** 's disease remain unknown. However, de novo administration of bromocriptine or lisuride to either l-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned primates or patients can alleviate **parkinsonian** symptoms without the development of dyskinesia. In this study, we have investigated behavioral responses and

alterations in the expression of opioid neuropeptide precursors preproenkephalin-A (PPE-A, encoding methionine- and leucine-enkephalin) and preproenkephalin-B (PPE-B), the precursor encoding dynorphins (dynorphin A1-17 and B1-13, leucine-enkephalin, and alpha-neoendorphin) in striatal output pathways of the 6-hydroxydopamine (6-OHDA)-lesioned rat model of **Parkinson**'s disease. Expression was assessed following repeated L-DOPA, bromocriptine, or lisuride administration. Given the functional organization of basal ganglia circuitry into anatomically discrete parallel circuits, we investigated alterations in peptide expression with reference to the detailed topography of the striatum. Following repeated L-DOPA administration (6.5 mg/kg, b.d., 21 days) in the 6-OHDA-lesioned rat a rotational response was observed. This became markedly enhanced with repeated **treatment**. We have previously characterized the pharmacology of this enhanced response and have suggested that it is a useful model for the elucidation of the cellular and molecular mechanisms underlying L-DOPA- and dopamine agonist-induced dyskinesia. In contrast to l-DOPA, de novo administration of bromocriptine (1 or 5 mg/kg, b.d., 21 days) or lisuride (0.01 or 0.1 mg/kg, b.d., 21 days) did not lead to an enhanced behavioral response. In vehicle-**treated** , 6-OHDA-lesioned animals, PPE-A expression was elevated rostrally and dorsally, while PPE-B expression was reduced in the striatum at all rostrocaudal levels. Repeated l-DOPA administration was accompanied by elevations in striatal PPE-B mRNA levels and a further elevation, above lesion-induced levels, in PPE-A expression. This further elevation was restricted to the dorsolateral striatum. However, following repeated bromocriptine or lisuride administration no increase in PPE-B expression was observed and the lesion-induced increase in PPE-A expression was normalized to prelesion levels. Increased PPE-A and PPE-B levels may, through decreasing **GABA** and glutamate release, respectively, in output nuclei of the basal ganglia, play a role in the development of L-DOPA- and dopamine-agonist induced dyskinesia in **Parkinson**'s disease. These studies suggest that anti-**parkinsonian treatments** which are not associated with an elevation in PPE-B and/or normalize elevated PPE-A precursor expression, such as NMDA-receptor antagonists or long-acting dopamine D2 receptor agonists, e.g., cabergoline or ropinirole, may reduce dyskinesia in **Parkinson**'s disease.

11/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10111625 98385921

Modulatory effects of L-DOPA on D2 dopamine receptors in rat striatum, measured using in vivo microdialysis and PET.

Opacka-Juffry J; Ashworth S; Ahier RG; Hume SP

PET Methodology Group, MRC Cyclotron Unit, Hammersmith Hospital, London, United Kingdom.

Journal of neural transmission (AUSTRIA) 1998, 105 (4-5) p349-64, ISSN 0300-9564 Journal Code: CIJ

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Putative modulatory effects of L-3,4-dihydroxyphenylalanine (L-DOPA) on D2 dopamine receptor function in the striatum of anaesthetised rats were investigated using both in vivo microdialysis and positron emission tomography (PET) with carbon-11 labelled raclopride as a selective D2 receptor ligand. A single dose of L-DOPA (20 or 100mg/kg i.p.) resulted in an increase in [11C]raclopride binding potential which was also observed in the presence of the central aromatic decarboxylase **inhibitor** NSD 1015, confirming that the effect was independent of dopamine. This L-DOPA evoked D2 receptor sensitisation was abolished by a prior, long-term administration of L-DOPA in drinking water (5 weeks, 170mg/kg/day). In the course of acute L-DOPA **treatment** (20mg/kg), extracellular **GABA** levels were reduced by approximately 20% in the globus pallidus. It is likely that L-DOPA sensitising effect on striatal D2 receptors, as

confirmed by PET may implicate striato-pallidal neurones, hence a reduced **GABA** -ergic output in the projection area. Since the L-DOPA evoked striatal D2 receptor supersensitivity habituates during long-term **treatment** , the effects reported here may contribute to the fluctuations observed during chronic L-DOPA therapy in **Parkinson**'s disease.

11/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10020165 99371145
Activation of nigral dopamine neurons by the selective **GABA** (B)-receptor antagonist SCH 50911.
Erhardt S; Nissbrandt H; Engberg G
Department of Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden.
Journal of neural transmission (AUSTRIA) 1999, 106 (5-6) p383-94, Journal Code: CIJ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Previous studies have shown that systemic as well as local administration of the **GABA** (B)-receptor agonist baclofen is associated with a decrease in firing rate, a regularisation of firing rhythm and a decrease in burst firing activity of dopamine (DA) containing midbrain neurons. In the present electrophysiological study we have utilised the novel, selective and potent **GABA**(B)-receptor antagonist SCH 50911 in order to further analyse the importance of **GABA** (B)-receptors for the overall activity of rat nigral DA neurons. SCH 50911 given intravenously (1-64 mg/kg) or locally, by microiontophoretic techniques, was found to increase firing rate and to increase the burst firing activity of DA neurons. The present data suggest that the **GABA** (B)-receptor antagonist blocks somatodendritic receptors on nigral DA neurons. This **GABA** -receptor input appears to be of a tonic nature. It is proposed that the activation of nigral DA neurons may underlie the beneficial effects of **GABA** (B)-receptor antagonists in the modulation of cognition and that **GABA**(B)-receptor antagonists may be of therapeutic value in the **treatment** of **Parkinson**'s disease.

11/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09978436 99299039
Post mortem studies in **Parkinson** 's disease--is it possible to detect brain areas for specific symptoms?
Jellinger KA
Ludwig Boltzmann Institute of Clinical Neurobiology, Vienna, Austria.
Journal of neural transmission (AUSTRIA) 1999, 56 p1-29, ISSN 0303-6995 Journal Code: JAK
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC
Parkinson 's disease (PD) is characterized by progressive neuronal loss associated with Lewy bodies in many subcortical nuclei leading to multiple biochemical and pathophysiological changes of clinical relevance. Loss of nigral neurons causing striatal dopamine deficiency is related to both the duration and clinical stages (severity) of the disease. The clinical subtypes of PD have different morphological lesion patterns: a) The akinetic-rigid type shows more severe cell loss in the ventrolateral part of substantia nigra zona compacta (SNZC) that projects to the dorsal putamen than the medial part projecting to caudate nucleus and anterior putamen, with negative correlation between SNZC cell counts, severity of akinesia-rigidity, and dopamine loss in the posterior putamen. Reduced

dopaminergic [redacted]but causes overactivity [redacted] the **GABA** ergic **inhibitory** striatal neurons projecting via the "indirect loop" to SN zona reticulata (SNZR) and medial pallidum (GPI) leading to **inhibition** of the glutamatergic thalamo-cortical motor loop and reduced cortical activation. b) The tremor-dominant type shows more severe neuron loss in medial than in lateral SNZC and damage to the retrorubral field A8 containing only few tyrosine hydroxylase and dopamine transporter immunoreactive (IR) neurons but mainly calretinin-IR cells. A8 that is rather preserved in rigid-akinetic PD (protective role of calcium-binding protein?) projects to the matrix of dorsolateral striatum and ventromedial thalamus. Together with area A10 it influences the strial efflux via SNZR to thalamus and from there to prefrontal cortex. Rest tremor in PD is associated with increased metabolism in the thalamus, subthalamus, pons, and premotor-cortical network suggesting an increased functional activity of thalamo-motor projections. In essential tremor, no significant pathomorphological changes but overactivity of cerebello-thalamic loop have been observed. c) In the akinetic-rigid forms of multisystem atrophy, degeneration is more severe in the lateral SNZC with severe loss of calbindin-IR cells reflecting initial degeneration of the striatal matrix in the caudal putamen with transsynaptic degeneration of striatonigral efferences that remain intact in PD. This fact and loss of striatal D2 receptors--as in advanced stages of PD--are reasons for negative response to L-dopa substitution. These data suggest different pathophysiological mechanisms of the clinical subtypes of PD that have important therapeutic implications. d) Involvement of extranigral structures in PD includes the mesocortical dopaminergic system, the noradrenergic locus coeruleus, dorsal vagal nucleus and medullary nuclei, serotonergic dorsal raphe, nucleus basalis of Meynert and other cholinergic brainstem nuclei, e.g. Westphal-Edinger nucleus (controlling pupillomotor function), posterolateral hypothalamus and the limbic system, e.g. amygdaloid nucleus, part of hippocampal formation, limbic thalamic nuclei with prefrontal projections, etc. Damage to multiple neuronal systems by the progressing degenerative process causing complex biochemical changes may explain the variable clinical picture of PD including vegetative, behavioural and cognitive dysfunctions, depression, pharmacotoxic psychoses, etc. Future comparative clinico-morphological and pathobiochemical studies will further elucidate the pathophysiological basis of specific clinical symptoms of PD and related disorders providing a broader basis for effective **treatment** strategies. **Parkinson**'s disease (PD) is characterized by progressive degeneration of the nigrostriatal dopaminergic system and other subcortical neuronal systems leading to striatal dopamine deficiency and other biochemical deficits related to the variable clinical signs and symptoms of the disorder. (ABSTRACT TRUNCATED)

11/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09914538 98445152

The effects of modafinil on striatal, pallidal and nigral **GABA** and glutamate release in the conscious rat: evidence for a preferential **inhibition** of striato-pallidal **GABA** transmission.

Ferraro L; Antonelli T; O'Connor WT; Tanganelli S; Rambert FA; Fuxe K

Department of Clinical and Experimental Medicine, University of Ferrara, Italy.

Neuroscience letters (IRELAND) Sep 4 1998, 253 (2) p135-8, ISSN 0304-3940 Journal Code: N7N

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The effects of the anti-narcoleptic drug modafinil (30-300 mg/kg i.p.) on **GABA** and glutamate release were evaluated in the basal ganglia of the conscious rat, by using the microdialysis technique. Modafinil (100 mg/kg) **inhibited** striatal (85+/-4% of basal values) and pallidal (85+/-2%) **GABA** release without influencing local glutamate release. At the

highest dose ([redacted] mg/kg), modafinil induced a f[redacted]ner reduction of pallidal (75+/-2%) but [redacted]ot striatal (82+/-7%) **GABA** [redacted]lease and increased striatal (134+/-11%) but not pallidal glutamate release. On the contrary, in the substantia nigra modafinil reduced **GABA** release only at the 300 mg/kg dose (59+/-5%) without affecting glutamate release. The preferential reduction in striato-pallidal **GABA** release at the 100 mg/kg dose of modafinil suggests that modafinil may be useful in the **treatment** of **Parkinsonian** diseases.

11/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09914090 99013981
Novel synthesis and release of **GABA** in cerebellar granule cell cultures after infection with defective herpes simplex virus vectors expressing glutamic acid decarboxylase.
New KC; Gale K; Martuza RL; Rabkin SD
Departments of Microbiology and Immunology, Georgetown University Medical Center, 3970 Reservoir Road NW, Washington, DC 20007, USA.
Brain research. Molecular brain research (NETHERLANDS) Oct 30 1998, 61 (1-2) p121-35, ISSN 0169-328X Journal Code: MBR
Contract/Grant No.: 2P30-CA-51008, CA, NCI; NS33342, NS, NINDS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The **inhibitory** amino acid neurotransmitter gamma-aminobutyric acid (**GABA**) is synthesized from glutamate in a single step by the enzyme glutamatic acid decarboxylase (**GAD**). We sought to determine whether viral vectors containing **GAD** cDNA could be used to enhance synthesis and stimulation-evoked release of **GABA** in cultures of CNS neurons. For this purpose, we generated double-cassette defective herpes simplex virus (HSV) vectors that expressed one of the two **GAD** isoforms (**GAD65** or **GAD67**), and Escherichia coli LacZ. Infection of cerebellar granule cell (CGC) cultures with vectors containing **GAD** cDNA resulted in a significant increase in isoform-specific expression of **GAD**, synthesis of **GABA**, and stimulation-evoked **GABA** release. **GAD65** and **GAD67** vector-infected neurons exhibited a comparable profile of **GABA** levels, synthesis and release, as well as **GAD** protein distribution. In CGCs cultured for 6 days in vitro (DIV), **GABA** synthesized after vector-derived **GAD** expression was released by **treatment** with glutamate or veratridine, but only in a Ca2+-independent fashion. In more mature (10 DIV) cultures, both Ca2+-dependent, K+ depolarization-induced, as well as Ca2+-independent, veratridine-induced, **GABA** release was significantly enhanced by **GAD** vector infection. **Treatment** of CGCs with kainic acid, which destroys most of the GABAergic neurons (<1% remaining), did not prevent vector-derived expression of **GAD** nor synthesis of **GABA**. This suggests that defective HSV vector-derived **GAD** expression can be used to increase **GABA** synthesis and release in CNS tissue, even in the relative absence of GABAergic neurons. The use of such **GAD** vectors in the CNS has potential therapeutic value in neurologic disorders such as epilepsy, chronic pain, **Parkinson** 's and Huntington's disease.

11/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09823500 99079264
Functional neuroanatomy of the basal ganglia as studied by dual-probe microdialysis.
O'Connor WT
Department of Human Anatomy and Physiology, University College, Dublin,

Ireland. wocon[redacted]eagh.ucd.ie
Nuclear medi[redacted]ne and biology (ENGLAND) Nov [redacted]98, 25 (8) p743-6, ISSN 0969-8051 Journal Code: BOO
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Dual probe microdialysis was employed in intact rat brain to investigate the effect of intrastriatal perfusion with selective dopamine D1 and D2 receptor agonists and with c-fos antisense oligonucleotide on (a) local **GABA** release in the striatum; (b) the internal segment of the globus pallidus and the substantia nigra pars reticulata, which is the output site of the strionigral **GABA** pathway; and (c) the external segment of the globus pallidus, which is the output site of the striopallidal **GABA** pathway. The data provide functional in vivo evidence for a selective dopamine D1 receptor-mediated activation of the direct strionigral **GABA** pathway and a selective dopamine D2 receptor **inhibition** of the indirect striopallidal **GABA** pathway and provides a neuronal substrate for parallel processing in the basal ganglia regulation of motor function. Taken together, these findings offer new therapeutic strategies for the **treatment** of dopamine-linked disorders such as **Parkinson**'s disease, Huntington's disease, and schizophrenia.

11/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09792036 99064131

Valproic acid relieved marked rigidity in three patients with end-stage **parkinsonism**]

Sayama S; Fujimoto K; Nakano I
Department of Neurology, National Sanatorium Ashikaga Hospital.
Rinsho shinkeigaku (JAPAN) Jun 1998, 38 (6) p495-8, ISSN 0009-918X Journal Code: DF2
Languages: JAPANESE Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE ; English Abstract

We applied valproic acid (VPA) on the rigidity of three **parkinsonian** patients, two with **Parkinson** disease and one with striatonigral degeneration. They were all at Hoehn and Yahr's stage V and showed marked rigidity. In these patients, effect of L-DOPA had become limited or increasing the dosage of L-DOPA was difficult because of its side effects. **Parkinsonian** symptoms were assessed by using motor score of Unified **Parkinson** 's Disease Rating Scale. The degree of rigidity in these three patients was markedly decreased with 300-600 mg/day of VPA. The blood level of VPA ranged from 24.8 to 66.5 micrograms/ml, which was relatively low compared with the effective blood level as an anti-epileptic agent. **Parkinsonian** symptoms other than rigidity, and the increased deep tendon reflexes which were present in the patient with striatonigral degeneration were not affected by VPA. Reduction of L-DOPA intensified rigidity again which had been under control. Trials of VPA on **parkinsonism** have been reported from two groups (Price PA, et al. 1978; Nutt J, et al. 1979), neither of which has observed any benefit of VPA. The difference of their results and ours seems to depend on the stage of patients; their patients had mild to moderate symptoms, whereas ours were in the end stage with marked rigidity. Since the effect of VPA upon **parkinsonism** is limited to rigidity, the end-stage patients whose care is difficult due to severe rigidity may obtain the best benefit of VPA. VPA is considered to take effect by activating gamma-aminobutyric acid (**GABA**) system. Because **GABA** is a common **inhibitory** neurotransmitter distributed in the wide areas of the central nervous system, it is difficult to locate the action site of VPA with regard to the amelioration of rigidity. The stretch reflex loop in the spinal cord does not seem to be the action site because no change was noted in deep tendon reflex. GABAergic striatal efferent neurons do not seem to be the sole action site either, because **parkinsonian** symptoms were not affected except for rigidity. The vestibular nucleus which receives strong GABAergic

afferents fro[redacted]cerebellar Purkinje cells is a[redacted]fficient tonus regulator. Since suppress[redacted]n of the function of the [redacted]cleus is known to reduce rigidity, it is at least a candidate for the action site of VPA. But there is no direct evidence for this matter. The exact action site of VPA remains to be elucidated.

11/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09495348 98218869
Increased survival of dopaminergic neurons by rasagiline, a monoamine oxidase B **inhibitor**.
Finberg JP; Takeshima T; Johnston JM; Commissiong JW
Department of Pharmacology, Faculty of Medicine, Technion, Haifa, Israel.
Neuroreport (ENGLAND) Mar 9 1998, 9 (4) p703-7, ISSN 0959-4965 Journal Code: A6M
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Both deprenyl and rasagiline (R(+)-N-propargyl-1-aminoindane mesylate), at a concentration of 1-10 microM, increased survival in vitro of rat E14 mesencephalic dopaminergic neurons that had been primed with 10% serum for 12 h ($p < 0.05$). Rasagiline, but not deprenyl, also increased total neuronal (MAP2-positive) survival ($p < 0.05$) Under serum-free conditions, rasagiline, but not deprenyl, retained its neuroprotective action on dopaminergic neurones. GABAergic neurons were not affected by either deprenyl or rasagiline. Clorgyline, an MAO-A **inhibitor**, did not exert any of these effects. The protective action of rasagiline on dopaminergic neurons, even under stringent serum-free conditions, is striking, and warrants further investigation for a role in the **treatment** of **Parkinson**'s disease.

11/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09397537 98109483
Metabolic **inhibition** enhances selective toxicity of L-DOPA toward mesencephalic dopamine neurons in vitro.
Nakao N; Nakai K; Itakura T
Department of Neurological Surgery, Wakayama Medical College, Japan.
Brain research (NETHERLANDS) Nov 28 1997, 777 (1-2) p202-9, ISSN 0006-8993 Journal Code: B5L
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Recent in vitro studies have described the toxicity of levodopa (L-DOPA) to dopamine (DA) neurons. We investigated whether metabolic **inhibition** with rotenone, an **inhibitor** of complex I of the mitochondrial respiratory chain, may enhance the toxicity of L-DOPA toward DA neurons in mesencephalic cultures. The uptakes of DA and **GABA** were determined to evaluate the functional and morphological integrity of DA and non-DA neurons, respectively. Pretreatment with rotenone significantly augmented the toxic effect of L-DOPA on DA neurons. Interestingly, prior metabolic **inhibition** with rotenone rendered DA cells susceptible to a dose (5 microM) of L-DOPA that otherwise exhibited no toxic effect. DA uptake was more intensely attenuated than **GABA** uptake after the combined exposure to rotenone and L-DOPA. This was confirmed by cell survival estimation showing that tyrosine hydroxylase-positive DA cells are more vulnerable to the sequential exposure to the drugs than total cells. The selective toxic effect of L-DOPA on rotenone-pretreated DA neurons was significantly blocked by antioxidants, but not antagonists of NMDA or non-NMDA glutamate receptors. This indicates that oxidative stress play a central role in mediating the selective damage of DA cells in the present

experimental paradigm. Our results raise the possibility that long-term L-DOPA **treatment** could accelerate the progression of degeneration of DA neurons in patients with **Parkinson** 's disease where potential energy failure due to mitochondrial defects has been demonstrated to take place.

11/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09336444 98005862
Adenosine A2A receptor antagonists as new agents for the **treatment** of **Parkinson**'s disease [see comments]
Richardson PJ; Kase H; Jenner PG
Pharmaceutical Development Centre, Kyowa Hakko Kogyo, Tokyo, Japan.
Trends in pharmacological sciences (ENGLAND) Sep 1997, 18 (9) p338-44, ISSN 0165-6147 Journal Code: WFT
Comment in Trends Pharmacol Sci 1998 Feb;19(2):46-8
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
There is now good reason to believe that blockade of the adenosine A2A receptor could be of value in the **treatment** of **Parkinson**'s disease. Peter J. Richardson, Hiroshi Kase and Peter G. Jenner review the actions of this receptor in the striatum, emphasizing its ability to modulate the neuronal activity of striatal **GABA**-releasing output neurones, and showing that recently developed A2A receptor antagonists are capable of reducing the disabling effects of nigral cell degeneration in primates. They conclude that such antagonists may be useful as novel therapeutic agents for the **treatment** of **Parkinson**'s disease.

11/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09308467 98004385
Effects of L-DOPA/carbidopa administration on the levels of L-DOPA, other amino acids and related compounds in the plasma, brain and heart of the rat.
Diederich C; Milakofsky L; Hare TA; Hofford JM; Dadmarz M; Vogel WH
Department of Pharmacology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA 19107, USA.
Pharmacology (SWITZERLAND) Sep 1997, 55 (3) p109-16, ISSN 0031-7012 Journal Code: P43
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Rats were **treated** intraperitoneally with a mixture of 250 mg/kg L-DOPA and 40 mg/kg carbidopa or with vehicle and sacrificed 30 min later. Plasma, heart and cortex, midbrain, brainstem and cerebellum were removed from each animal and assayed by HPLC for L-DOPA and a large number of amino acids and related amino compounds. L-DOPA levels increased from undetectable (<0.2 nmol/ml or g) to 1,146, 1,007, 399, 376, 368 and 850 nmol/ml or g in the above tissues. In addition, several amino compounds were significantly affected by L-DOPA/carbidopa ($p < \text{or} = 0.01$). Plasma concentrations of phosphoserine, oxidized glutathione, citrulline, phenylalanine, tyrosine and 1-methylhistidine increased and arginine, glutamic acid and lysine decreased. In the heart, concentrations of phosphoserine, taurine, reduced glutathione, threonine, serine, glutamine, glycine, alanine, valine, **GABA**, ethanolamine, ammonia and arginine decreased. In the cortex, camosine and homocarnosine increased. In the midbrain, valine increased and leucine, ornithine and oxidized glutathione decreased. In the cerebellum, citrulline increased. In the brainstem, threonine, serine, asparagine, glutamine, oxidized glutathione, alanine, and leucine decreased. In the brainstem, arginine was slightly decreased

with a concomitant increase in citrulline ($p < [illegible]$), indicative of nitrous oxide formation. These results show that administration of L-DOPA/carbidopa not only raises dopamine levels but can also affect other biochemicals and that the observed changes in amino acids and related compounds can perhaps contribute to the beneficial and/or adverse effects of L-DOPA/carbidopa therapy of **Parkinson**'s disease.

11/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08975071 97142232
New horizons in molecular mechanisms underlying **Parkinson**'s disease and in our understanding of the neuroprotective effects of selegiline.
Gerlach M; Desser H; Youdim MB; Riederer P
Neurologische Klinik, Ruhr-Universitat Bochum, Germany.
Journal of neural transmission (AUSTRIA) 1996, 48 p7-21, ISSN 0303-6995 Journal Code: JAK
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
There have been many claims that the selective monoamine oxidase type B (MAO-B) **inhibitor** selegiline may have distinct properties in slowing the progression of **Parkinson**'s disease (PD). Degeneration of nigro-striatal dopaminergic neurons is the primary histopathological feature of PD. Although many different hypotheses have been advanced, the cause of chronic nigral cell death and the underlying mechanisms remain elusive as yet. Therefore, there is no clear knowledge regarding an understanding of the reported effects of selegiline on the progression of PD. However, there is a considerable body of indirect evidence that oxidative stress may play a role in the pathogenesis of this illness. Oxidative stress refers to cytotoxic consequences of hydrogen peroxide and oxygen-derived free radicals such as the hydroxyl radical (.OH), the superoxide anion (.O2), and nitric oxide (NO), which are generated as byproducts of normal and aberrant metabolic processes that utilize molecular oxygen. On the other hand, an increasing body of experimental data has implicated excitotoxicity as a mechanism of cell death in both acute and chronic neurological disease. One of the receptor which is particularly involved in the toxic effects of excitatory amino acids is the NMDA (N-methyl-D-aspartate) receptor. Excessive stimulation of this type of receptor by glutamic acid or NMDA agonists leads to a massive influx of calcium ions into the neuron followed by activation of a variety of calcium-dependent enzymes, impaired mitochondrial function, and the generation of free radicals. This article will consider the concept that excitotoxicity is linked with the generation of free radicals. In view of this idea it will be further discussed how selegiline might exert its neuroprotective effects via indirect actions on the polyamine binding site of the NMDA receptor. Under **treatment** with the MAO-B **inhibitor** selegiline, the degradation of putrescine via MAO, a key factor in regulating the polyamine metabolism, might be diminished in the **Parkinsonian** brain, which in turn would suppress the polyamine synthesis. Hence, the reported neuroprotective effect of selegiline might also receive a contribution from the diminished potentiation of the NMDA receptor by the polyamine binding site. On the other hand, since N1-acetylated spermine and spermidine are also good substrates of MAO-B, it is likely that these compounds will be present in the brain in increased concentrations. It therefore seems possible that they will exert a neuroprotective effect via an antagonistic modulation of the polyamine binding site of the NMDA receptor.

11/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08707430 96176

Consequences of nigrostriatal denervation on the gamma-aminobutyric acidic neurons of substantia nigra pars reticulata and superior colliculus in **parkinsonian** syndromes.

Vila M; Herrero MT; Levy R; Faucheux B; Ruberg M; Guillen J; Luquin MR; Guridi J; Javoy-Agid F; Agid Y; Obeso JA; Hirsch EC

INSERM U289, Hopital de la Salpetriere, Paris, France.

Neurology (UNITED STATES) Mar 1996, 46 (3) p802-9, ISSN 0028-3878 Journal Code: NZ0

Languages: ENGLISH

Document type: JOURNAL ARTICLE

To examine the effects of nigrostriatal denervation on the substantia nigra pars reticulata (SNpr), one of the main outputs of the basal ganglia, we used quantitative in situ hybridization to analyze the messenger RNA coding for Mr 67,000 glutamic acid decarboxylase (**GAD67** mRNA) in the SNpr neurons from patients with **Parkinson**'s disease (PD), monkeys rendered **parkinsonian** by 1-methyl-4- phenyl-1,2,3,6-tetrahydropyridin e (MPTP), and their respective controls. In MPTP-intoxicated monkeys, the expression of **GAD67** mRNA was increased in the SNpr neurons, and the increase was reversed by L-dopa **treatment**. There were no differences in the level of **GAD67** mRNA between PD patients who had been **treated** with L-dopa and control subjects. Combined with the previously reported increased expression of **GAD67** mRNA in the internal segment of the pallidum of MPTP-intoxicated monkeys, these data suggest that the gamma-aminobutyric acid (GABAergic) activity of the output system of the basal ganglia is globally increased by nigrostriatal denervation. We also analyzed the level of **GAD67** mRNA expression in the superior colliculus, a structure that receives the **inhibitory** influence of the GABAergic neurons of the SNpr and that is involved in eye movement control. **GAD67** mRNA expression was reduced in both MPTP-intoxicated monkeys, whether or not they received L-dopa therapy, and PD patients, compared to their respective controls. This decrease may result from the hyperactivity of the **inhibitory** nigrotectal pathway, but also from other influences since it was not corrected by L-dopa therapy. These changes may account for the slight ocular motor and visuospatial cognitive impairment occurring in PD, even after L-dopa therapy.

11/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08664155 96217972

Modulation of **GABA** transmission by diazoxide and cromakalim in the globus pallidus: implications for the **treatment** of **Parkinson**'s disease.

Maneuf YP; Duty S; Hille CJ; Crossman AR; Brotchie JM

Division of Neuroscience, School of Biological Sciences, University of Manchester, United Kingdom.

Experimental neurology (UNITED STATES) May 1996, 139 (1) p12-6, ISSN 0014-4886 Journal Code: EQF

Languages: ENGLISH

Document type: JOURNAL ARTICLE

An ATP-sensitive potassium channel (KATP) is known to modulate insulin release from pancreatic beta cells. It has been proposed that potassium channels related to KATP in the nervous system might similarly modulate neurotransmitter release. We have therefore investigated the effects of KATP opening agents on **GABA** release in the globus pallidus. Diazoxide and cromakalim decreased the K(+)-evoked release of [3H]**GABA** from pallidal slices. The maximum **inhibition** observed for diazoxide (59%) and cromakalim (66%) was achieved at a concentration of 100 microM. The effects of both cromakalim and diazoxide were significantly antagonized by the concurrent application of the sulfonylurea glibenclamide (100 microM). Intrapallidal injections of diazoxide in the reserpine-**treated** rat

model of **Parkinson** 's disease reduced akinesia in a dose-dependent manner. These data suggest that manipulation of neuronal potassium channels with pharmacological properties similar to KATP may prove useful in the **treatment** of **Parkinson**'s disease.

11/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08500143 96130869
An endogenous dopaminergic neurotoxin: implication for **Parkinson**'s disease.
Mattammal MB; Haring JH; Chung HD; Raghu G; Strong R
Geriatric Research, Educational and Clinical Center, VA Medical Center, St. Louis, Missouri 63125, USA.
Neurodegeneration (ENGLAND) Sep 1995, 4 (3) p271-81, ISSN 1055-8330 Journal Code: B99
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Oxidation of dopamine by monoamine oxidase results in the endogenous metabolite 3,4-dihydroxyphenylacetaldehyde (DOPAL). The toxicity of DOPAL for dopaminergic neurons was investigated using rat neostriatal synaptosomes, PC-12 cells and cultures of fetal rat dissociated mesencephalon. The Na(+)-dependent uptake of [3H]DOPAL in synaptosomes was **inhibited** by mazindol. DOPAL selectively **inhibited** dopamine uptake but not [14C]**GABA** uptake, induced membrane damage and liberation of dopamine into the medium. Incubation of PC-12 cells with 6.5 microM of DOPAL for 24 h caused degeneration of the neuritic process, and the number of viable cells were reduced by 25% of control. There were practically no surviving cells after 24 h of incubation with 33 microM of DOPAL. After 8 h of **treatment** with 33 microM of DOPAL, dopamine and 3,4-dihydroxyphenylacetic acid content in the cells were reduced by 38% and 53% of control. DOPAL-induced cell damage released lactic acid dehydrogenase into the incubation media. This toxic effect of DOPAL was time- and concentration-dependent. In mesencephalic cultures, after exposure to 33 microM of DOPAL, the surviving TH+ cells showed rounded cell body, and fibre network was highly reduced. These results indicate DOPAL is a neurotoxin and may be involved in the degeneration of dopaminergic neurons.

11/3,AB/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08200064 94198278
Neurotransmitter replacement therapy in Alzheimer's disease.
Mohr E; Mendis T; Rusk IN; Grimes JD
Institute of Mental Health Research, University of Ottawa, Ontario, Canada.
Journal of psychiatry & neuroscience (CANADA) Jan 1994, 19 (1) p17-23, ISSN 1180-4882 Journal Code: A0C
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
The relative success of symptomatic attenuation of motor dysfunction in **Parkinson** 's disease with dopaminomimetics has spurred interest in neurotransmitter replacement therapy for **treating** Alzheimer's disease. While cholinergic dysfunction has been linked to various clinical parameters in Alzheimer's disease, cholinergic replacement, including precursor therapy, administration of direct-acting agonists and **inhibition** of enzymatic degradation has had only very modest success. The **inhibition** of enzymatic degradation has perhaps shown the most interesting results to date. However, conclusions with respect to efficacy continue to be controversial. Discussion continues about whether or not

single transmitter replacement for Alzheimer's disease is a viable **treatment** approach. Deficiencies in central noradrenergic, serotonergic, GABAergic and perhaps dopaminergic neural transmission may also play a critical role in some of the clinical manifestations of Alzheimer's disease. In addition, certain neuropeptides, in particular somatostatin, may be important in this context. Several series of clinical trials are currently attempting to address these issues. Given the complexities of the pathophysiology of Alzheimer's disease, symptomatic relief may require multiple transmitter replacement and necessitate more definitive intercessions at the molecular biological level.

11/3,AB/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07863483 94126193
Chronic CY 208-243 **treatment** of MPTP-monkeys causes regional changes of dopamine and GABAA receptors.
Gagnon C; Gomez-Mancilla B; Bedard PJ; Di Paolo T
School of Pharmacy, Laval University, Que., Canada.
Neuroscience letters (IRELAND) Nov 26 1993, 163 (1) p31-5, ISSN 0304-3940 Journal Code: N7N
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Four monkeys were rendered **parkinsonian** by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) i.v. administration and then **treated** chronically with increasing doses of the D1 agonist CY 208-243 (0.05, 0.1 and 0.5 mg/kg). All animals showed a dose-dependent improvement of their **parkinsonian** signs after the chronic CY 208-243 **treatment**; however, half of them developed peak-dose dyskinesias. Dopamine levels were more decreased in the striatum of MPTP-monkeys with dyskinesias compared to those without dyskinesias. [3H]SCH 23390 and [3H]SKF 38393 binding to D1 receptors were in general similar in the striatum of both groups of MPTP-monkeys except [3H]SKF 38393 binding which was lower in the posterior putamen of dyskinetic compared to non-dyskinetic monkeys reflecting decreased coupling of this receptor to G proteins. [3H]spiperone and [3H]N-n-propylnorapomorphine binding to D2 receptors in the striatum tended in general to be higher in dyskinetic compared to non-dyskinetic monkeys, and this reached statistical significance in the posterior caudate labelled with [3H]n-propylnorapomorphine. [3H]muscimol binding to GABAA receptors was significantly higher in the posterior caudate of dyskinetic compared to non-dyskinetic monkeys. The extent of striatal DA denervation, decreased D1, elevated D2 and GABAA receptors, as well as the decrease of the D1/D2 receptor ratio in the posterior striatum may be involved in the appearance of dyskinesias after chronic CY 208-243 **treatment**.

11/3,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07798144 93233197
Brain-derived neurotrophic factor selectively rescues mesencephalic dopaminergic neurons from 2,4,5-trihydroxyphenylalanine-induced injury.
Skaper SD; Negro A; Facci L; Dal Toso R
Fidia Research Laboratories, Fidia S.p.A., Abano Terme, Italy.
Journal of neuroscience research (UNITED STATES) Mar 1 1993, 34 (4) p478-87, ISSN 0360-4012 Journal Code: KAC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Brain-derived neurotrophic factor (BDNF) supports the survival of sensory neurons as well as retinal ganglion cells, basal forebrain cholinergic neurons, and mesencephalic dopaminergic neurons in vitro. Here we examined the ability of BDNF to confer protection on cultured dopaminergic neurons

against the neurotoxic effects of 6-hydroxyDOPA (TOPA or 2,4,5-trihydroxyphenylalanine), a metabolite in the dopamine pathway suggested to participate in the pathology of **Parkinson**'s disease. Cells prepared from embryonic day 14-15 rat mesencephalon were maintained with 10-50 ng/ml BDNF for 7 days prior to addition of TOPA (10-30 microM) for 24 hr. In BDNF-**treated** cultures, the extensive loss (> 90%) of tyrosine hydroxylase immunopositive cells was virtually (< 10%) eliminated, while the equally drastic loss (> 90%) of the overall cell population was limited to only a 25-30% recovery. Furthermore, the monosialoganglioside GM1 (1-10 microM), although inactive alone, acted synergistically with subthreshold amounts of BDNF to rescue tyrosine hydroxylase-positive cells against TOPA neurotoxicity. These results add impetus to exploring the therapeutic potential of gangliosides and BDNF in **Parkinson** 's disease.

11/3,AB/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07757459 93137245
An animal model for coexisting tardive dyskinesia and tardive **parkinsonism**: a glutamate hypothesis for tardive dyskinesia.
Gunne LM; Andren PE
Department of Psychiatry, Uller.ANG.aker, Uppsala University, Sweden.
Clinical neuropharmacology (UNITED STATES) Feb 1993, 16 (1) p90-5, ISSN 0362-5664 Journal Code: CNK
Languages: ENGLISH
Document type: JOURNAL ARTICLE
There is now ample evidence for long-term malfunctioning within five different brain GABAergic pathways in a monkey model for tardive dyskinesia (TD). Three of these **GABA** connections (GPe-STN, CP-SNr, and CP-GPi) are chronically downregulated during neuroleptic **treatment** and after some years they do not seem to regain their normal activity, even when the neuroleptics are discontinued. The persistent downregulation of these three **GABA** connections, evidenced by depressions of terminal **GAD** activity and **GABA** levels, appears to be a conceivable mechanism behind tardive **parkinsonism** (TP), often reported to coexist with TD in the clinic. The TD patients' well-known lack of awareness of their symptoms may be due to their **parkinsonian** "sensory neglect." Another two **GABA** malfunctioning connections were found in our monkey model: SNr-VA/VL and GPi-VA/VL. These pathways are upregulated during chronic neuroleptic **treatment** , partly due to an elevated glutamate release within subthalamofugal pathways. This chronic glutamatergic hyperactivity may have acted via an excitotoxic mechanism and consequently both GPi and VA/VL had a low synaptic activity in our dyskinetic monkeys, as measured by 2-deoxyglucose uptake, even 4 months after the last neuroleptic dose. It is hypothesized that TD may be due to an excitotoxic lesion of the **inhibitory** GABAergic VA/VL afferents, while TP has to do with persistent malfunctioning of downregulated SNr and GPi afferents.

11/3,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07706015 94105401
Dopaminergic regulation of glutamic acid decarboxylase mRNA expression and **GABA** release in the striatum: a review.
Lindefors N
Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden.
Progress in neuro-psychopharmacology & biological psychiatry (ENGLAND) Nov 1993, 17 (6) p887-903, ISSN 0278-5846 Journal Code: Q45
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

1. The maj y of neurons in the striat (caudate-putamen, dorsal striatum; nuc accumbens, ventral striatum) nd in striatal projection regions (the pallidum, the entopeduncular nucleus and substantia nigra reticulata) use gamma-aminobutyric acid (**GABA**) as transmitter and express glutamic acid decarboxylase (**GAD**; rate limiting enzyme) in the synthesis of **GABA**. **GABA** is the major **inhibitory** transmitter in the mammalian brain. 2. **GAD** in brain is present as two isoenzymes, **GAD65** and **GAD67**. **GAD65** is largely present as an inactive apoenzyme, which can be induced by nerve activity, while most **GAD67** is present as a pyridoxal phosphate-bound permanently active holoenzyme. Thus **GAD65** and **GAD67** seem to provide a dual system for the control of neuronal **GABA** synthesis. 3. **GAD** mRNA expression can be visualised and quantified using in situ hybridisation, and **GABA** release can be quantified using in vivo microdialysis. 4. Different populations of **GABA** neurons can be distinguished in both dorsal and ventral striatum as well as in other parts of the basal ganglia. 5. **Inhibition** of dopaminergic transmission in the striatum by lesion of dopamine neurons or by neuroleptic **treatment** is followed by an increased release of **GABA** and increased expression of **GAD67** mRNA in a subpopulation of striatal medium-sized neurons which project to the globus pallidus, and increased striatal **GAD** enzyme activity. 6. Increased dopaminergic transmission by repeated but not single doses of amphetamine is followed by decreased striatal **GABA** release and decreased **GAD67** mRNA expression in a subpopulation of medium-sized neurons in the striatum. 7. Two populations of medium-sized **GABA** neurons in the striatum seem to be under tonic dopaminergic influence. The majority of these **GABA** neurons are under **inhibitory** influence, whereas a small number seem to be stimulated by dopamine. 8. Specific changes in activity in subpopulations of striatal **GABA** neurons probably mediate the dopamine-dependent hypokinetic syndrome seen in **Parkinson**'s disease and following neuroleptic **treatment**.

11/3,AB/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07470666 92291749
Gamma vinyl **GABA** in the **treatment** of levodopa-induced dyskinesias in **Parkinson**'s disease [letter]
Turjanski N; Lees AJ
Journal of neurology, neurosurgery, and psychiatry (ENGLAND) May 1992, 55 (5) p413, ISSN 0022-3050 Journal Code: JBB
Languages: ENGLISH
Document type: LETTER

11/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07456851 91347950
Vigabatrin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy and disorders of motor control [published erratum appears in Drugs 1991 Aug;42(2):330]
Grant SM; Heel RC
Adis Drug Information Services, Auckland, New Zealand.
Drugs (NEW ZEALAND) Jun 1991, 41 (6) p889-926, ISSN 0012-6667 Journal Code: EC2
Languages: ENGLISH
Document type: CLINICAL TRIAL; JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC
Vigabatrin was specifically designed to enhance gamma-aminobutyric acid (**GABA**) function in the CNS. By increasing brain concentrations of this **inhibitory** neurotransmitter the drug appears to decrease propagation of abnormal hypersynchronous discharges, thereby reducing seizure activity.

At this stage in its development, clinical experience with vigabatrin is limited primarily to patients with refractory seizure disorders. In this difficult-to-**treat** population, 'add-on' therapy with vigabatrin greater than or equal to 2 g/day has shown impressive efficacy, reducing seizure frequency by greater than or equal to 50% in approximately half of patients. Clinical efficacy does seem to vary with seizure type with the best response reported in adults with complex partial seizures with or without generalisation and in children with cryptogenic partial epilepsy or symptomatic infantile spasm. Vigabatrin appears to have a negative effect on absences and myoclonic seizures. Some disorders of motor control may also be amenable to enhanced GABAergic function. In the small number of patients with tardive dyskinesia **treated** to date, vigabatrin produced mild to moderate improvement in hyperkinetic symptom scores but **Parkinsonism** or schizophrenic symptoms occasionally worsened. The best response was reported in a study of patients who had been withdrawn from neuroleptic therapy. In a small but well-controlled comparative trial, vigabatrin was as effective as baclofen in reducing spasm and improving some parameters of spasticity in patients with spinal cord lesions or multiple sclerosis. Most adverse reactions to vigabatrin are mild and transient with central nervous system (CNS) changes being reported most frequently. Of particular note, serial evoked potential studies and the few available histology reports have not found evidence of intramyelinic oedema during therapeutic use, as was reported in rats and dogs on chronic high-dose **treatment** . Thus, vigabatrin is a promising new anticonvulsant drug. Current evidence supports a trial of this agent as adjunctive therapy in patients with refractory seizure disorders, and future investigation of vigabatrin monotherapy and its efficacy relative to established agents is awaited with interest. Wider experience should help to clarify which patients - by seizure type and concurrent CNS pathology - are likely to benefit from vigabatrin and ongoing monitoring should further clarify the potential detrimental effects, if any, of long term use. In the meantime, it is a welcome addition in the difficult setting of resistant epilepsy.

11/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06905251 92061644
N-methyl-D-aspartate antagonists in the **treatment** of **Parkinson**'s disease [see comments]
Greenamyre JT; O'Brien CF
Department of Neurology, University of Rochester Medical Center, NY 14642.
Archives of neurology (UNITED STATES) Sep 1991, 48 (9) p977-81, ISSN 0003-9942 Journal Code: 80K
Contract/Grant No.: S7RR05403-29, RR, NCRR
Comment in Arch Neurol 1992 Sep;49(9):900-1
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Current long-term **treatment** of **Parkinson** 's disease is inadequate, and improved symptomatic and neuroprotective therapies are needed. Recent interest has focused on the use of antagonists of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor in **Parkinson**'s disease. Abnormally increased activity of the subthalamic nucleus is postulated to play a central pathophysiological role in the signs of **Parkinson** 's disease, and NMDA antagonists may provide a means of decreasing this activity selectively. Like dopaminergic agonists, NMDA antagonists can reverse the akinesia and rigidity associated with monoamine depletion or neuroleptic-induced catalepsy. Very low doses of NMDA antagonists markedly potentiate the therapeutic effects of dopaminergic agonists. There is evidence that the beneficial effects of anticholinergic drugs and amantadine may be mediated, in part, by NMDA receptor blockade. Moreover, NMDA antagonists provide profound protection

of dopaminer[redacted] neurons of the substa[redacted]a nigra in the MPTP (1-methyl-4-phe[redacted]l-1,2,3,6-tetrahydropyridine) [redacted]d methamphetamine models of **Parkinson** 's disease. The clinical use of NMDA antagonists may prove useful in **Parkinson**'s disease to **treat** symptoms and retard disease progression.

11/3,AB/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06306239 87071888
Neurobiologic and pharmacologic studies on the pathogenesis of **Parkinson** disease]
Neurobiologische und pharmakologische Untersuchungen zur Pathogenese der **Parkinson**-Krankheit.
Brucke T; Riederer P
Wiener medizinische Wochenschrift (AUSTRIA) Aug 31 1986, 136 (15-16) p401-8, ISSN 0043-5341 Journal Code: XOU
Languages: GERMAN Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE ; English Abstract
Parkinson 's disease is characterized especially by a degeneration of pigmented brain regions, like substantia nigra. These changes are accompanied by a variety of biochemical disturbances of dopaminergic and noradrenergic systems. Also the reduction of serotonin can be related to degenerative processes occurring in subareas of the raphe. Furthermore amino acid transmitters like **GABA** and a variety of peptidergic neuromodulators are changed. Additional cholinergic hypofunction due to degeneration of the nucleus basalis Meynert is able to impair the quality of life due to loss of intellectual capacity. A variety of biochemical mechanisms compensate for a long time the progression of neuronal loss. Modern **treatment** strategies (combined L-dopa therapy, dopaminergic agonists, MAO-B **inhibitors** , amantadine) are able to substitute the deficiency especially of the catecholamines. For the development of more causal therapies, a new animal model has been developed 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes **parkinsonism% %% after peripheral administration and leads to denervation of the dopaminergic nigrostriatal system. It is the hope that this new model, which is described here in detail, will lead to decisive data underlying the cause of** Parkinson's **disease.**

11/3,AB/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06026544 86067528
New central dopamine agonists.
Borsy J
Polish journal of pharmacology and pharmacy (POLAND) May-Jun 1985, 37 (3) p227-36, ISSN 0301-0244 Journal Code: PBO
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW
Recently, the importance of the dopamine receptor agonists has increased in the treatment **of** parkinsonism, **different endocrinological diseases and cardiovascular illness. In the therapy some well known drugs, derivatives of ergot groups e.g. bromocriptine, lisuride and pergolide, have been found useful. In the Institute for Drug Research numerous semi-synthetic elymoclavine derivatives were synthesized during the past years, and the influence of these new compounds on both the central and peripheral dopamine transmission was examined. Among the different ergot derivatives compound GYKI-32 887 seemed to be the most effective dopamine agonist and it was selected for preclinical investigation. The endocrinological effects and the pre- and postsynaptic dopamine receptor stimulant activity of this new compound are summarized. GYKI-32 887 was**

more potent than bromocriptine as regards its inhibitory effect on prolactin secretion and antiparkinsonian efficacy. Besides the strong dopamine receptor stimulant action this new ergoline compound, contrary to bromocriptine, inhibits the convulsive action of bicucullin. It may be assumed that the GABA receptor agonistic effect of GYKI-32 887 would be also valuable in the treatment of various form of dyskinesias.

11/3,AB/34 (Item 34 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04646514 83274261
Effect of gamma-vinyl GABA in tardive dyskinesia.
Korsgaard S; Casey DE; Gerlach J
Psychiatry research (NETHERLANDS) Apr 1983, 8 (4) p261-9, ISSN 0165-1781 Journal Code: QC4
Languages: ENGLISH
Document type: JOURNAL ARTICLE
gamma-Vinyl GABA (gamma-aminobutyric acid), a drug that increases brain GABA via GABA transaminase inhibition , was evaluated in a blind, placebo-controlled trial in 10 patients with stable tardive dyskinesia. Drug effects during active treatment (2 to 6 g/day) and during pre- and posttreatment placebo periods were determined by scoring randomly sequenced videotapes of tardive dyskinesia and parkinsonian symptoms recorded weekly during standardized examinations. Tardive dyskinesia was significantly reduced, and correlated to increased parkinsonism . Eye blinking rates decreased, but psychiatric symptoms were unchanged during treatment.

11/3,AB/35 (Item 35 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04621790 81109522
Side effects in preventive maintenance therapy with neuroleptics with special emphasis on tardive dyskinesia.
Logothetis J; Paraschos A; Frangos E
Bibliotheca psychiatrica (SWITZERLAND) 1981, (160) p22-9, ISSN 0067-8147 Journal Code: 9W8
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Neuroleptics induce hypersensitivity reactions, and toxic, systemic and extrapyramidal manifestations. The latter mainly include acute dystonic reactions, other early dyskinesias, akathisia, parkinsonism and TD. These drugs have been implicated for DA antagonism exerted by an adenylate cyclase inhibition. Prolonged blockade of DA receptors is considered as the motivation for a counterbalancing mechanism inducing the DA supersensitivity from which TD results. Recent reports suggest cholinergic and GABA ergic insufficiency as secondary participants. The increasing frequency of TD calls for prevention by modifying treatment practices and searching for effective measures to combat the symptoms.

11/3,AB/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04621155 81085316
gamma-Acetylenic GABA in tardive dyskinesia.
Casey DE; Gerlach J; Magelund G; Christensen TR
Archives of general psychiatry (UNITED STATES) Dec 1980, 37 (12)

p1376-9, ISSN [redacted]03-990X Journal Code: 72C
Contract/Gra[redacted]No.: 14081
Languages: ENGLISH
Document type: CLINICAL TRIAL; CONTROLLED CLINICAL TRIAL; JOURNAL ARTICLE
Brain gamma-aminobutyric acid (GABA) has been proposed to play a role in the modulation of extrapyramidal motor function. The effects of increasing brain GABA with gamma-acetylenic GABA (GAG), a drug that inhibits GABA transaminase, were evaluated in ten patients with stable tardive dyskinesia during a blind placebo-controlled trial. Drug effects during active treatment and two placebo periods were evaluated by scoring randomly sequenced videotapes of tardive dyskinesia and parkinsonian symptoms recorded weekly during a standardized examination. Tardive dyskinesia was significantly reduced, and preexisting parkinsonism increased slightly. The largest decrease in tardive dyskinesia symptoms occurred in patients receiving higher neuroleptic doses, suggesting an interaction between GABA and dopamine. Prolactin values increased but growth hormone values were unchanged. Psychiatric symptoms were also unchanged during GAG treatment.

11/3,AB/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04345637 83064304
Pharmacodynamic effects and possible therapeutic uses of THIP, a specific GABA-agonist.
Christensen AV; Svendsen O; Krogsgaard-Larsen P
Pharmaceutisch weekblad. Scientific edition (NETHERLANDS) Oct 22 1982, 4 (5) p145-53, ISSN 0167-6555 Journal Code: OZW
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW
THIP (4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol) is a potent and specific GABA receptor agonist which does not influence the GABA uptake system or GABA metabolizing enzymes. The specificity for the GABA receptor is also demonstrated by lack of action on monoaminergic, cholinergic, histaminergic or opiate receptors. Since in recent years GABA receptor stimulants-among others THIP--have become available many have speculated as to what clinical indication GABA-ergic stimulation might be an important element. The first suggestion was that GABA-ergic drugs by an inhibitory effect on the dopamine neurons would improve the antischizophrenic effect of neuroleptics and improve tardive dyskinesia. Furthermore, studies on brains of deceased Parkinson and Huntington's chorea patients have demonstrated a low level of GABA and its synthesizing enzyme glutamic acid decarboxylase (GAD) in the basal ganglia. Also in epilepsy and diseases with dementia a deficit in the GABA system has been proposed. Therefore a therapeutic strategy for these diseases may be supplementary treatment with drugs which increase GABA receptor activity. Furthermore, recent results in humans have shown that GABA agonists perhaps also could be of benefit in mania and depressions. When considering the neurophysiological elements of nociception and muscle tone it is also reasonable to suggest that GABA-ergic stimulation may reduce pain perception and muscle tone.

11/3,AB/38 (Item 38 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

03890170 83234879
Alterations in apomorphine concentration in spinal cord and brain follow the time course of catalepsies induced by different treatments.
Kolasiewicz W; Harasiewicz A; Melzacka M; Wolfarth S
Experimental neurology (UNITED STATES) Jul 1983, 81 (1) p195-209,

ISSN 0014-4886 Journal Code: EQF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Because evidence for the neurotransmitter role of dopamine in the gray matter of the spinal cord is accumulating, a question arises of whether or not spinal dopamine receptors are also involved in the effects of dopaminomimetics which are believed to induce beneficial effects in Parkinson 's disease through an action thought to be mediated mainly by striatal dopamine receptors. To test this hypothesis muscimol and picrotoxin were injected unilaterally into the posterior part of the substantia nigra of rabbits permanently implanted with stainless-steel cannulae. Muscimol (a GABA -mimetic) enhanced locomotor activity, evoked a stereotyped behavior and contralateral rotations, and increased apomorphine-induced gnawing. Picrotoxin, a substance which inhibits GABA transmission, induced ipsilateral rotations, evoked catalepsy and muscle rigidity, and inhibited locomotor activity. Picrotoxin abolished apomorphine-induced gnawing, and increased haloperidol-mediated catalepsy. The catalepsy induced by an intranigral injection of picrotoxin, and the picrotoxin-evoked blockade of the apomorphine-induced gnawing disappeared within 16 h after the intranigral injection. Alterations in the apomorphine concentration in brain structures (n. caudatus and cerebral cortex) and in spinal cord after picrotoxin injection followed the same time course as the behavioral changes, and returned to the control values 16 h after injection of picrotoxin. Apomorphine was always injected 30 min before the rabbits were killed. Moreover, the substantial increase (to 300%) in apomorphine concentration in the spinal cord probably reflects the antagonism between behavioral changes induced by picrotoxin and the haloperidol catalepsy, rather than the decreased apomorphine concentrations observed in the brain structures. We suggest, therefore, that there exists a correlation between the behavioral effects, which are generally accepted as laboratory models of Parkinson 's disease, and the enhanced apomorphine concentration in the spinal cord.

11/3,AB/39 (Item 39 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

03269688 79243183
The pathogensis and medical treatment of extrapyramidal disease.
Calne DB; Eisler T
Medical clinics of North America (UNITED STATES) Jul 1979, 63 (4) p715-27, ISSN 0025-7125 Journal Code: LU6
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW

11/3,AB/40 (Item 40 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

03212938 80084809
Effects of GABA-analogues on the high-affinity uptake of GABA in astrocytes in primary cultures.
Schousboe A
Advances in experimental medicine and biology (UNITED STATES) 1979, 123 p219-37, ISSN 0065-2598 Journal Code: 2LU
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Employing primary cultures of astrocytes which seem to constitute a valid model of their in vivo counterparts, it has been demonstrated that this cell type is likely to be of importance in terminating the transmitter activity of GABA . It has been shown that the transport carrier in astrocytes is stereospecific for the C-4 hydrogens of the GABA molecule and that its structural requirements are distinct from those

exhibited by [redacted] neuronal GABA carrier. beta-P[redacted]ine was a selective inhibitor of GABA transport in astro[redacted]es, whereas R-trans-4-methyl-4-aminocrotonic acid and S-nipecotic acid seemed to be selective inhibitors of neuronal GABA transport, as studied using very thin slices ("prisms") of brain cortex. These findings may be important for studies on the relative significance of the two transport systems in GABA -mediated neurotransmission, and thus for future pharmacological manipulations of the GABA system. This may eventually be beneficial for the treatment of neurological disorders such as epilepsy, Huntington's chorea and Parkinson's disease in which the GABA system seems to be disturbed (34,60,62).

11/3,AB/41 (Item 41 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

02890971 80022477
Treatment of Parkinson 's disease with sodium valproate: clinical, pharmacological, and biochemical observations.
Nutt J; Williams A; Plotkin C; Eng N; Ziegler M; Calne DB
Canadian journal of neurological sciences (CANADA) Aug 1979, 6 (3) p337-43, ISSN 0317-1671 Journal Code: CJ9
Languages: ENGLISH
Document type: CLINICAL TRIAL; JOURNAL ARTICLE
Because there is biochemical evidence of decreased GABAergic function in Parkinson's disease, sodium valproate, an inhibitor of GABA catabolism, was administered to eight Parkinsonian patients. Valproate treatment did not significantly alter any Parkinsonian feature, but tended to increase the dyskinesia in the "on-off" patients. The increased dyskinesias were not a result of altered peripheral metabolism of L-dopa. Despite obtaining high plasma levels of valproate, no consistent alteration of CSF GABA levels could be demonstrated. Thus, in these patients, an effect of valproate on GABA metabolism is unproven, and in turn, the role of GABA in Parkinsonism and dyskinesia uncertain.

11/3,AB/42 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12672824 BIOSIS NO.: 200000426326
The 5HT1B receptor agonist, CP-93129, inhibits (3H)-GABA release from rat globus pallidus slices and reverses akinesia following intrapallidal injection in the reserpine-treated rat.
AUTHOR: Chadha Anita; Sur Cyrille; Atack John; Duty Susan(a)
AUTHOR ADDRESS: (a)Neurodegenerative Disease Research Group, Wolfson Centre for Age-Related Diseases, GKT School of Biomedical Sciences, King's College London, Hodgkin Building, London, SE1 1UL**UK
JOURNAL: British Journal of Pharmacology 130 (8):p1927-1932 August, 2000
MEDIUM: print
ISSN: 0007-1188
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: 1 This study examined whether activation of 5HT1B receptors in the rodent globus pallidus (GP) could reduce GABA release in vitro and reverse reserpine-induced akinesia in vivo. 2 Microdissected slices of GP from male Sprague Dawley rats (300-350 g) were preloaded with (3H)-GABA. During subsequent superfusion, 4 min fractions were collected for analysis of release. The effects of the 5HT1B receptor agonist, 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo(3,2-b)pyrid-5-one (CP-93129), on

25 mM KCl-evoked release were examined using a standard dual stimulation paradigm. 3 M[redacted] Sprague Dawley rats (270-290 [redacted] stereotaxically cannulated above the GP, were rendered akinetic by injection of reserpine (5 mg kg-1 s.c.). Eighteen hours later, the rotational behaviour induced by unilateral injection of CP-93129 was examined. 4 CP-93129 (0.6-16.2 muM) produced a concentration-dependent inhibition of 25 mM KCl-evoked (3H)-GABA release reaching a maximum inhibition of 52.5+-4.5%. The effect of a submaximal concentration of CP-93129 (5.4 muM) was fully inhibited by the 5HT1B receptor antagonist, isamoltane (10 muM). 5 Following intrapallidal injection, CP-93129 (30-330 nmol in 0.5 mul) produced a dose-dependent increase in net contraversive rotations reaching a maximum of 197+-32 rotations in 240 min at 330 nmol. Pre-treatment with isamoltane (10 nmol in 1 mul) inhibited the effects of a submaximal dose of CP-93129 (220 nmol) by 84+-6%. 6 These data suggest that at least some 5HT1B receptor function as heteroreceptors in the GP, reducing the release of GABA . Moreover, CP-93129-mediated activation of these receptors in the GP provides relief of akinesia in the reserpine-treated rat model of PD.

11/3,AB/43 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12537331 BIOSIS NO.: 200000290833
4-aminotetrahydrobenzisoxazole or -isothiazole compounds.
AUTHOR: Falch Erik(a); Perregaard Jens Kristian; Schousboe Arne; Krogsgaard-Larsen Povl; Frolund Bente; Moltzen Lenz Sibylle
AUTHOR ADDRESS: (a)Vedbaek**Denmark
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1229 (1):pNo pagination Dec. 7, 1999
MEDIUM: e-file.
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The present invention relates to novel 4-aminotetrahydrobenzisoxazoles or 4-aminotetrahydrobenziothiazoles having gamma-aminobutanoic acid (GABA)-uptake inhibiting activity and thus useful in the treatment of analgesia, psychosis, convulsions, anxiety, epileptic disorders or muscular and movement disorders, such as spastic disorders or symptoms in Huntington's disease or Parkinson disease.

11/3,AB/44 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11986120 BIOSIS NO.: 199900266639
Dopaminomimetic psychosis in Parkinson's disease patients: Diagnosis and treatment.
AUTHOR: Wolters Erik Ch(a)
AUTHOR ADDRESS: (a)Department of Neurology, Academic Hospital, Vrijc Universiteit, 1007 MB, Amsterdam**Netherlands
JOURNAL: Neurology 52 (7 SUPPL. 3):pS10-S13 1999
ISSN: 0028-3878
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Dopaminomimetic agents, which were rationally designed to reverse

dopamine defi[redacted]s in the substantia nigra and ventral tegmental area of the parkinson[redacted] midbrain, effectively attenua[redacted] deficits in motor and non-motor behavior thought to be elicited by dopamine deficiencies in the striatal and frontal limbic regions, respectively. On the other hand, dopaminomimetic medications may also induce perturbations in postsynaptic peptides, causing dopaminergic hypersensitivity. Drug-induced chronic dopaminomimetic psychosis afflicts about one-fifth of PD patients on dopaminergic regimens. Although the long-held mechanism for psychosis in PD is excessive stimulation of mesocorticolimbic dopamine receptors, interactions between dopamine and serotonin, as well as participation of serotonin-modulated GABAergic neurons may also contribute to the pathophysiology. Reduction or withdrawal of anticholinergic agents, amantadine, and dopamine precursors or agonists constitutes a first approach to the problem but is often insufficient. Unfortunately, typical antipsychotic agents such as haloperidol, which selectively antagonizes dopamine D-2 receptors, can induce extrapyramidal syndromes such as tardive parkinsonism. On the other hand, emerging atypical neuroleptics such as clozapine, quetiapine, and olanzapine, which antagonize 5HT-2A receptors (among others), inhibit D-2 receptors to a lesser degree and exhibit selective binding to mesolimbic (vs. striatal) dopamine receptors. The limbic selectivity of these agents appears to be of greater magnitude than that typical of risperidone. In addition, the selective antiserotonergic agent ondansetron is a prospective therapeutic option. The pharmacologic properties of these agents are explored.

11/3,AB/45 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11976738 BIOSIS NO.: 199900230051
Recommendations for drug therapy of Parkinson's disease based on the experiences after the Bochum conference February 6; 1998.
AUTHOR: Przuntek H(a); Mueller Th
AUTHOR ADDRESS: (a)Neurologische Klinik, St. Josef-Hospital, Ruhr-Universitaet Bochum, Gudrunstr. 56, 44791, Bochum**Germany
JOURNAL: Aktuelle Neurologie 25 (SUPPL. 4):pS344-S346 Dec., 1998
ISSN: 0302-4350
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: German; Non-English
SUMMARY LANGUAGE: English; German

ABSTRACT: Early diagnosis of idiopathic Parkinson's disease is essential for sufficient therapy. One must crucially discuss, whether levodopa still remains the gold standard in all stages of the disease due to results of animal trials suggesting the toxicity of levodopa in the damaged brain. Moreover long term application of levodopa induces occurrence of motor complications, such as fluctuations and dyskinesias, both of which do not result from other antiparkinsonian drugs. Therefore early therapy with dopamine agonists and non-dopaminergic drugs gains more and more importance. Combination therapy with substitution of levodopa with dopamine agonists to an extent of at least 30 to 40% should be performed in the case of necessity of levodopa application. Moreover combination of levodopa and dopamine agonists makes sense due to the clinical observation of decreasing efficacy of monotherapy with dopamine agonists within a certain time period. Both catechol-O-methyl-transferase-inhibitors, tolcapone and entacapone, are novel therapeutic strategies after the occurrence of motor complications, such as fluctuations. The question of advantages for one of both catechol-O-methyl-transferase-inhibitors remains unsolved due to the lacking comparative studies in the same individuals. Liver toxicity and diarrhoea may occur after application of tolcapone but not entacapone. Animal trials demonstrated neuroprotective properties of the

MAO-B-inhibit[redacted]selegiline. Clinical studies showed that addition of selegiline[redacted] levodopa may induce levodopa [redacted]ring effect, but all these clinical trials did not demonstrate the neuroprotective efficacy of selegiline in parkinsonian subjects. But application of selegiline may be neuroprotective especially in early stages of the disease. Amantadine gains importance due to results of retrospective trials discussing a reduction of mortality and neuroprotective properties, but both have to be confirmed by further convincing studies. The novel drug budipine may support efficacy of all known symptomatic therapies, because budipine possesses a polyvalent receptor profile influencing various neurotransmitters, such as GABA, NMDA, norepinephrine, serotonine, dopamine and acetylcholine. Moreover budipine may antagonize the toxicity of MPTP- and MPP+, but neuroprotective efficacy still have to be proven clinically. Budipine is efficous and superior to other drugs used for treatment of parkinsonian tremor. Stimulation of growth factors and/or transplantation of mesencephalic neuronal grafts may represent new promising anti-parkinsonian therapies, but their proof of efficacy still lacks. Treatment of non motor symptoms, such as seborrhoea, hypotonina, gastrointestinal dysfunction, sleep- and mood disturbances and cognitive dysfunction, is also very essential beside improvement of the classical extrapyramidal symptomatology, such as akinesia, tremor and rigidity, in parkinsonian subjects.

11/3,AB/46 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11227582 BIOSIS NO.: 199800008914
Neurotoxicity and possible roles of aspartic acid, glutamic acid and GABA in some neurologic disorders.
AUTHOR: Qureshi G Ali(a); Baig Shahid M; Parvez S H
AUTHOR ADDRESS: (a)Clinical Research Center, Huddinge Univ. Hosp., Novum, S-141 57 Huddinge**Sweden
JOURNAL: Biogenic Amines 13 (6):p565-578 1997
ISSN: 0168-8561
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In this study, the role of excitatory amino acids; aspartic (ASP) and glutamic acid (GLU), and GABA is defined on the basis of accumulated results obtained in cerebrospinal fluid (CSF) from 88 patients with neurological disorders such as Parkinson's disease (PD) (n=20), cerebrovascular disorder (CVD) (n=16), multiple sclerosis (MS) (n=20), tuberculous meningitis (TBM) (n=14) and aseptic meningitis (AM) (n=18). These results are compared with data from healthy subjects (n=14). The results show significant CSF increase of ASP, GLU and GABA in all these groups except in MS patients where decrease in ASP, GLU and GABA was observed. There is a linear relationship between CSF GLU and nitrite in PD, CVD and TBM patients suggesting these two parameters are interrelated, promoting the possibility for the design of therapeutic approaches consisting of GLU release inhibitors and EAA antagonists and free radical scavengers for treatment of these neurologic disorders with effectivity.

11/3,AB/47 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10672684 BIOSIS NO.: 199799293829
Dopaminergic inhibition of striatal GABA release after 6-hydroxydopamine.
AUTHOR: Harsing Laszlo G Jr; Zigmond Michael J(a)

AUTHOR ADDRESS: (a)Dep. Neuroscience, Univ. Pittsburgh, 570 Crawford Hill, Pittsburgh, [redacted]5260**USA
JOURNAL: Brain Research 738 (1):p142-145 1996
ISSN: 0006-8993
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have examined the regulation of striatal GABA release by endogenous dopamine in rats with partial degeneration of dopamine-containing neurons. 6-Hydroxydopamine was administered into the lateral ventricles or medial forebrain bundle. Either 3 days or 3 weeks later, slices of neostriatum were prepared, preloaded with (3H)GABA , and superfused in order to measure (3H)GABA overflow in response to electrical stimulation (8 Hz). The loss of dopaminergic terminals was estimated by measuring tissue levels of dopamine. The impact of endogenous dopamine on (3H)GABA was evaluated by measuring the ability of sulpiride, a D-2 dopamine receptor antagonist, to increase the depolarization-induced (3H)GABA overflow. In non-treated or vehicle-pretreated rat neostriatum, sulpiride (10 mu-M) increased the depolarization-induced (3H)GABA overflow to 193% of control. Three days after lesioning, the stimulatory effect of sulpiride on (3H) GABA overflow was identical to that seen in control rats so long as the loss of tissue dopamine did not exceed 60%, although with larger lesions the sulpiride-induced response was reduced. Three weeks after lesioning, however, the stimulatory effect of sulpiride on electrically evoked (3H)GABA overflow remained at the level seen in control tissue even in cases where tissue dopamine was reduced to 13% of normal. In contrast, no sulpiride-induced increase in (3H)GABA overflow was detected 3 weeks after nearly complete lesions which reduced tissue dopamine to 2% of normal. These data suggest that short- and long-term compensatory changes maintain dopaminergic control over GABAergic projection neurons and interneurons until the loss of dopamine innervation is almost complete.

11/3,AB/48 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10016685 BIOSIS NO.: 199598471603
A selective toxicity toward cultured mesencephalic dopaminergic neurons is induced by the synergistic effects of energetic metabolism impairment and NMDA receptor activation.
AUTHOR: Marey-Semper Isabel(a); Gelman Michele; Levi-Strauss Matthieu
AUTHOR ADDRESS: (a)INSERM U114, Coll. France, 11 Place Marcelin Berthelot, 75231 Paris Cedex 05**France
JOURNAL: Journal of Neuroscience 15 (9):p5912-5918 1995
ISSN: 0270-6474
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Numerous observations strongly support the hypothesis that dopaminergic neurons could be particularly vulnerable to an impairment of their energetic metabolism. In order to demonstrate the existence of such a selective vulnerability, the toxic effects of rotenone, an inhibitor of complex I of the respiratory chain, and of glutamate, which is very likely involved in the neurotoxicity induced by an energetic stress, were analyzed on cultured mouse mesencephalic neurons. Toxicity toward dopaminergic and GABAergic neurons was compared by measuring the residual uptakes of dopamine and GABA. Exposure to 5 nm rotenone for 6 hr or to a low concentration of glutamate (100 mu-M) for 1 hr did not lead to a high selective toxic effect on dopaminergic neurons. In contrast, dopaminergic neurons were three times less resistant to the sequential exposure to rotenone and glutamate than

GABAergic neurons. A particular resistance of mesencephalic GABAergic neurons to the synergistic toxic effects of rotenone and glutamate was ruled out since two other neuronal types, the striatal cholinergic and GABAergic neurons, displayed the same weak vulnerability as the mesencephalic GABAergic neurons. This selective toxic effect of glutamate on rotenone-pretreated dopaminergic neurons was blocked by either AMPA or NMDA receptor antagonists and mimicked by combined treatment with AMPA and NMDA, or by NMDA alone when the medium was deprived of Mg-2+ ions. Moreover, this NMDA-selective neurotoxicity was critically dependent on the presence of a physiological extracellular sodium concentration, since the use of choline chloride instead of sodium chloride had a protective effect on dopaminergic neurons. Our results indicate that both the activation of NMDA receptors and the impairment of the energetic metabolism induce a selective toxicity toward mesencephalic dopaminergic neurons. This could therefore explain their natural degeneration in the course of Parkinson's disease, in which mitochondrial abnormalities have been recently described.

11/3,AB/49 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09926906 BIOSIS NO.: 199598381824
Toxic effects of L-DOPA on mesencephalic cell cultures: Protection with antioxidants.
AUTHOR: Pardo B; Mena M A(a); Casarejos M J; Paino C L; De Yebenes J G
AUTHOR ADDRESS: (a)Lab. Monoaminas, Dep. Investigacion, Hosp. Ramon Cajal, Madrid**Spain
JOURNAL: Brain Research 682 (1-2):p133-143 1995
ISSN: 0006-8993
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The toxicity of L-3,4-dihydroxyphenylalanine (L-DOPA) -as studied in neuronal cultures from rat mesencephalon. The survival and function of DA neurons were assessed by the number of tyrosine hydroxylase-positive (TH+) cells and 3H-DA uptake and those non-DA neurons by the exclusion of Trypan blue and the high-affinity 3H-GABA uptake. L-DOPA was toxic for both DA and non-DA neurons. DA neurons were more severely affected than non-DA neurons after short periods of treatment and with exposure to a low dose of L-DOPA (25 vs. 100 mu-M) and less selectively affected after 1 or 2 days of treatment. After incubation with L-DOPA, a disruption of the neuritic network and an overall deterioration were observed, more evident for TH+ cells in the whole culture. Auto-oxidation to quinones is responsible in part for L-DOPA toxicity in non-DA neurons since the levels of quinones correlated well with the severity of cell death in the cultures. The damage of DA neurons took place before the rising of quinones, suggesting that quinones are not essential in L-DOPA toxicity for DA neurons. Antioxidants, such as ascorbic acid and sodium metabisulfite, completely prevented L-DOPA-induced quinone formation as well as the death of non-DA neurons. In contrast, they could only partially prevent the damage produced by L-DOPA in DA neurons. Mazindol, a selective inhibitor of DA uptake, protected TH+ cells from L-DOPA.

11/3,AB/50 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08975664 BIOSIS NO.: 199396127165
Some aspects of the synaptic circuitry underlying inhibition in the ventrobasal thalamus.

AUTHOR: Ohara P[redacted](a); Lieberman A R
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JOURNAL: Journal of Neurocytology 22 (9):p815-825 1993
ISSN: 0300-4864
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We describe here, and review, the ultrastructural features and synaptic relationships of flat-vesicle containing, presumptively inhibitory presynaptic elements in the glomerular and extraglomerular neuropils of the thalamic ventrobasal (VB) nucleus in monkey, cat and rat. This account is based on EM study of normal material, LM and EM immunocytochemistry for GABA, anterograde tracing with HRP and EM of physiologically characterized interneurons intracellularly injected with HRP. It emerges clearly from this study that attempts to categorize flat-vesicle containing terminals in thalamic tissue as either F-boutons (axon terminals with flattened synaptic vesicles and Gray type II synaptic specializations) or P-boutons (dendritic appendages of interneurons with flattened vesicles) by examining only single sections are likely to produce unreliable results. In many cases it is only by studying serial sections that such profiles can be unambiguously identified. Within glomeruli the P-boutons participate in triplet (triadic) synapses which are thought to mediate rapid feed forward inhibition of projection cells, and serial synaptic arrays involving other P-boutons. Since P-boutons from more than one interneuron are present in individual VB glomeruli, P-bouton to P-bouton synapses may mediate disinhibition of interneurons. We show that dendritic shafts of interneurons make and receive synaptic contacts and that in the monkey, at least, reciprocal synaptic contacts between shafts or between a shaft and a P-bouton are not uncommon. Finally, we confirm that in the rat VB there are insignificant numbers of P-boutons or cells with the morphological and transmitter characteristics of interneurons and we suggest that comparative electrophysiological studies of inhibitory events in rat VB versus those in cat or monkey VB during transmission of somatosensory information might help to clarify the roles of thalamic intrinsic neurons.

11/3,AB/51 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

05724152 BIOSIS NO.: 000084072558
ADAPTATION OF THE GABA-A-RECEPTOR COMPLEX IN RAT BRAIN DURING CHRONIC ELEVATION OF GABA BY ETHANOLAMINE O SULFATE
AUTHOR: LINDGREN S; SIMMONDS M A
AUTHOR ADDRESS: DEP. MED. PHARMACOL., BOX 593, BIOMEDICUM, S-751 UPPSALA, SWEDEN.
JOURNAL: BR J PHARMACOL 91 (3). 1987. 617-626.
FULL JOURNAL NAME: British Journal of Pharmacology
CODEN: BJPCB
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Slice preparations of rat cuneate nucleus were used for studies on the .gamma.-aminobutyric acid GABAA-receptor complex following chronic and acute pretreatment with GABA-.alpha.-ketoglutarate aminotransferase (GABA-T) inhibitors. The whole brain GABA concentration was significantly increased 2.9 fold and 2.6 fold following treatment with ethanolamine O-sulphate (EOS, orally) for 15-30 days and 56-64 days, respectively. One hour after a single injection of .gamma.-acetylenic GABA (GAG) i.p., there was a significant 2.1 fold increase in whole brain GABA. Superfusion of a

slice with muscimol or the GABA uptake inhibitor nipecotic acid depolarized the afferent nerve fibres. These effects were potentiated by flurazepam (1 .mu.M) and pentobarbitone (10 .mu.M) and antagonized by picrotoxin (3 .mu.M, 30 .mu.M). Following 15-30 days of EOS-treatment, the depolarization response to muscimol was decreased and that to nipecotic acid increased. These changes were no longer significant by 56-64 days of pretreatment. The acute dose of GAG did not affect the depolarization response to muscimol but increased that to nipecotic acid. The potentiations of muscimol by flurazepam (1 .mu.M) and pentobarbitone (10 .mu.M) were enhanced following chronic EOS treatment (15-64 days). The enhancement of flurazepam was less after 56-64 days than after 15-30 days pretreatment whereas the enhancement of pentobarbitone was similar at both times. Acute GAG treatment had no effect. The potency of picrotoxin as an antagonist of muscimol was reduced following chronic EOS pretreatment; the enhancement was less after 56-64 days than 15-30 days pretreatment. Acute GAG treatment caused only a very small reduction in picrotoxin potency. Possible adaptations in the GABAA-receptor complex and its modulation during chronic elevation of brain GABA are discussed.

11/3,AB/52 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

03989514 BIOSIS NO.: 000076075080
EFFECT OF GAMMA VINYL GAMMA AMINO BUTYRIC-ACID IN TARDIVE DYS KINESIA
AUTHOR: KORSGAARD S; CASEY D E; GERLACH J
AUTHOR ADDRESS: DEP. H., SCT. HANS MENTAL HOSPITAL, DK-4000, ROSKLIDE, DENMARK.
JOURNAL: PSYCHIATRY RES 8 (4). 1983. 261-270.
FULL JOURNAL NAME: Psychiatry Research
CODEN: PSRSD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: gamma.-Vinyl GABA, a drug that increases brain GABA via GABA transaminase inhibition, was evaluated in a blind, placebo-controlled trial in 10 patients with stable tardive dyskinesia. Drug effects during active treatment (2-6 g/day) and during pre- and posttreatment placebo periods were determined by scoring randomly sequenced videotapes of tardive dyskinesia and parkinsonian symptoms recorded weekly during standardized examinations. Tardive dyskinesia was significantly reduced and correlated to increased parkinsonism. Eye blinking rates decreased, but psychiatric symptoms were unchanged during treatment.

11/3,AB/53 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

03906490 BIOSIS NO.: 000075084563
BEHAVIORAL AND BIOCHEMICAL CHANGES CAUSED BY MUSCIMOL IN MICE WITHDRAWN FROM HALOPERIDOL ADMINISTRATION
AUTHOR: KURUVILLA A; FUNG Y K; URETSKY N J
AUTHOR ADDRESS: DIV. PHARMACOL., COLL. PHARMACY, OHIO STATE UNIV., COLUMBUS, OHIO 43210, USA.
JOURNAL: NEUROPHARMACOLOGY 21 (9). 1982. 891-898.
FULL JOURNAL NAME: Neuropharmacology
CODEN: NEPHB
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Recently, many investigators have been concerned with the study

of the pharmacological effects of prolonged neuroleptic therapy. After chronic administration of neuroleptic drugs, extrapyramidal side effects are produced which change in intensity over time. Parkinsonian side effects occur acutely but gradually disappear as tolerance develops, while tardive dyskinesias develop over a more prolonged period and usually increase in intensity when the neuroleptic drug is withdrawn. The neurochemical basis of these temporal changes is not clear. The behavioral and biochemical effects of the GABA agonist muscimol were studied in mice withdrawn from chronic haloperidol administration. Mice received haloperidol or vehicle in their drinking water for 35 days, after which the haloperidol was replaced with vehicle. Seven days after withdrawal from chronic treatment with haloperidol, the effect of apomorphine on the climbing behavior of haloperidol-withdrawn mice was markedly enhanced as compared to control mice that received only vehicle. Muscimol produced a dose-related reduction in the intensity of climbing behavior induced by apomorphine in both control and haloperidol-withdrawn mice. The inhibition of climbing behavior induced by muscimol was significantly greater in haloperidol-withdrawn animals. In haloperidol-withdrawn mice, muscimol produced a significant reduction in striatal homovanillic (HVA) levels with no change in striatal dopamine (DA) levels, suggesting a decrease in DA turnover. Muscimol decreased the disappearance of DA in haloperidol-withdrawn mice that were injected with .alpha.-methyl-p-tyrosine. Both the behavioral and biochemical effects of muscimol were blocked by the GABA antagonist picrotoxin. After chronic haloperidol administration, there is not only an enhanced response to dopaminergic agonists but also to GABAergic agonists.

11/3,AB/54 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

03243167 BIOSIS NO.: 000071056278
GAMMA ACETYLENIC GAMMA AMINO BUTYRIC-ACID IN TARDIVE DYS KINESIA
AUTHOR: CASEY D E; GERLACH J; MAGELUND G; CHRISTENSEN T R
AUTHOR ADDRESS: DEP. PSYCHIATRY, VETERANS ADM. MED. CENT., SAM JACKSON PARK, PORTLAND, OREG. 97201, USA.
JOURNAL: ARCH GEN PSYCHIATRY 37 (12). 1980 (RECD. 1981). 1376-1379.
FULL JOURNAL NAME: Archives of General Psychiatry
CODEN: ARGPA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Brain GABA may play a role in the modulation of extrapyramidal motor function. The effects of increasing brain GABA with .gamma.-acetylenic GABA (GAG), a drug that inhibits GABA transaminase, were evaluated in 10 patients with stable tardive dyskinesia during a blind placebo-controlled trial. Drug effects during active treatment and 2 placebo periods were evaluated by scoring randomly sequenced videotapes of tardive dyskinesia and parkinsonian symptoms recorded weekly during a standardized examination. Tardive dyskinesia was significantly reduced, and preexisting parkinsonism increased slightly. The largest decrease in tardive dyskinesia symptoms occurred in patients receiving higher neuroleptic doses, suggesting an interaction between GABA and dopamine. Prolactin values increased with growth hormone values were unchanged. Psychiatric symptoms were also unchanged during GAG treatment.

11/3,AB/55 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

02765041 BIOSIS NO.: 000068075652

INHIBITORS OF [redacted]MA AMINO BUTYRIC-ACID METABOLI[redacted]
AUTHOR: METCALF B W
AUTHOR ADDRESS: CENT. RECH. MERRELL INT., 16 RUE D'ANKARA, 67084 STRASBOURG, FR.
JOURNAL: BIOCHEM PHARMACOL 28 (11). 1979. 1705-1712.
FULL JOURNAL NAME: Biochemical Pharmacology
CODEN: BCPCA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The recognition of .gamma.-aminobutyric acid (GABA) as a major inhibitory neurotransmitter in the mammalian CNS stimulated the search for drugs such as GABA receptor agonists, GABA uptake inhibitors and inactivators of 4-aminobutyrate:2-oxoglutarate aminotransferase (GABA-T, EC 2.6.1.19), the GABA catabolizing enzyme, which may potentiate GABA neurotransmission. Such agents may be useful in treating several diseases in which a deficiency of GABA function has been demonstrated or implicated, e.g., Huntingdon's disease, tardive dyskinesia, Parkinsonism, epilepsy and schizophrenia. Of course, as GABA itself does not readily cross the blood brain barrier, its oral administration would not correct a deficiency of GABA in brain. During the last 10 yr a new concept of enzyme inhibition has been enunciated. This concept requires that the inhibitor contain a latent reactive functionality which is liberated as a result of the target enzyme's own mechanism of action. Such inhibitors, which have been designated suicide enzyme inactivators, are expected to be highly-specific because they should inhibit only those enzymes which can accept them as substrates. Several inhibitors, which function by a mechanism requiring activation by GABA-T prior to that enzyme's irreversible inactivation, have recently been designed and synthesized or isolated from natural resources. It is the intent of this commentary to describe the status of inhibitors of GABA metabolism from a mechanistic, and hence specificity, viewpoint.

11/3,AB/56 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE

10589753 EMBASE No: 2000054495
Axolemmal transporters for neurotransmissor uptake
TRANSPORTADORES AXOLEMALES PARA LA CAPTACION DE NEUROTRANSMISORES
Garcia-Lopez M.
Prof. M. Garcia-Lopez, Inst. Farmacologia Teofilo Hernando, Departamento de Farmacologia, Universidad Autonoma de Madrid, Arzobispo Morcillo 4, E-28029 Madrid Spain
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Revista de Neurologia (REV. NEUROL.) (Spain) 01 DEC 1999, 29/11 (1056-1063)
CODEN: RVNRA ISSN: 0210-0010
DOCUMENT TYPE: Journal; Review
LANGUAGE: SPANISH SUMMARY LANGUAGE: ENGLISH; SPANISH; PORTUGUESE
NUMBER OF REFERENCES: 54

Introduction and objective. Neurotransmission is a fundamental process in interneuronal communication. It starts with the release of the neurotransmitter following a nerve impulse and ends either by uptake by specific specific transporters or by metabolization to an inactive compound. In this review we will consider the molecular, ion dependence and electrogenic properties of the axolemal transporters for neurotransmitters and also the pathological consequences of their impairment as well as the drugs that can interact with them. Development. Most axolemmal transporters have been cloned and grouped into two large families according to their molecular characteristics and electrogenic properties: 1. Those dependent

on Nasup +/Cl [redacted]lude transporters of GABA, nor[redacted]enaline, dopamine, serotonin, choline, proline, betaine, glycine and taurine, and 2. Those dependent on Nasup +/Ksup + which include the transporters of glutamate, alanine, serine and cysteine. Conclusions. The clonation of transporters has permitted (and will continue to permit) the correlation of molecular alterations of transporters with different neuro-degenerative disorders (e.g. multiple sclerosis, Parkinson's disease. Alzheimer's disease), with brain lesions (e.g. cerebral ischemia, status epilepticus) and with psychiatric alterations (e.g. schizophrenia, depression). In this respect, chemical synthesis of new selective drugs which interact with the different systems for uptake of neurotransmitters will offer new approaches to the treatment of many disorders of the central nervous system which still have no satisfactory, drug treatment.

11/3,AB/57 (Item 2 from file: 72)
DIALOG(R)File 72:EMBASE

07715063 EMBASE No: 1999207455
Group I metabotropic glutamate receptors: Implications for brain diseases
Bordi F.; Ugolini A.
F. Bordi, Pharmacology Department, Glaxo Wellcome Med. Research Center, 37100 Verona Italy
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Progress in Neurobiology (PROG. NEUROBIOL.) (United Kingdom) 1999, 59/1 (55-79)
CODEN: PGNBA ISSN: 0301-0082
PUBLISHER ITEM IDENTIFIER: S0301008298000951
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 322

Glutamate is the major excitatory neurotransmitter in the brain and plays a unique role in a variety of central nervous system (CNS) functions. The discovery of the metabotropic receptors (mGluRs), a family of G-protein coupled receptors than can be activated by glutamate, has led to an impressive number of studies in recent years aimed at understanding their biochemical, physiological and pharmacological characteristics. The eight mGluRs now known are divided into three groups according to their sequence homology, signal transduction mechanisms, and agonist selectivity. Group I mGluRs include mGluRinf 1 and mGluR$D5, which are linked to the activation of phospholipase C; Groups II and III include all others and are negatively coupled to adenylyl cyclases. The availability in recent years of agents selective for Group I mGluRs has made possible the study of the physiological roles of these receptors in the CNS. In addition to mediating glutamatergic neurotransmission, Group I mGluRs can modulate other neurotransmitter receptors, including GABA and the ionotropic glutamate receptors. Group I mGluRs are involved in many CNS functions and may participate in a variety of disorders such as pain, epilepsy, ischemia, and chronic neurodegenerative diseases. This class of receptor may provide important pharmacological therapeutic targets and elucidating its functions will be relevant to develop new treatments for neurological and psychiatric disorders in which glutamatergic neurotransmission is abnormally regulated. In this review anatomical, physiological and pharmacological results are presented with a special emphasis on the role of Group I mGluRs in functional and pathological processes.

11/3,AB/58 (Item 3 from file: 72)
DIALOG(R)File 72:EMBASE

07062931 EMBASE No: 1997344788
Neurotoxicity and possible roles of aspartic acid, glutamic acid and

GABA in some n[redacted]logic disorders
Ali Qureshi G.; Baig S.M.; Parvez S.H.
G. Ali Qureshi, Clinical Research Center, Huddinge University Hospital, Novum, S-141 57 Huddinge Sweden
Biogenic Amines (BIOG. AMINES) (Netherlands) 1997, 13/6 (565-578)
CODEN: BIAME ISSN: 0168-8561
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 76

In this study, the role of excitatory amino acids; aspartic (ASP) and glutamic acid (GLU), and GABA is defined on the basis of accumulated results obtained in cerebrospinal fluid (CSF) from 88 patients with neurological disorders such as Parkinson's disease (PD) (n = 20), cerebrovascular disorder (CVD) (n = 16), multiple sclerosis (MS) (n = 20), tuberculous meningitis (TBM) (n = 14) and aseptic meningitis (AM) (n = 18). These results are compared with data from healthy subjects (n = 14). The results show significant CSF increase of ASP, GLU and GABA in all these groups except in MS patients where decrease in ASP, GLU and GABA was observed. There is a linear relationship between CSF GLU and nitrite in PD, CVD and TBM patients suggesting these two parameters are interrelated, promoting the possibility for the design of therapeutic approaches consisting of GLU release inhibitors and EAA antagonists and free radical scavengers for treatment of these neurologic disorders with effectivity.

11/3,AB/59 (Item 4 from file: 72)
DIALOG(R)File 72:EMBASE

06738774 EMBASE No: 1997020245
Preclinical studies with modafinil. Evidence for vigilance enhancement and neuroprotection
Fuxe K.; Rambert F.A.; Ferraro L.; O'Connor W.; Laurent P.; Agnati L.F.; Tanganelli S.
K. Fuxe, Dept. of Neuroscience, Div. Cellular/Molecular Neurochem., Karolinska Inst., Stockholm Sweden
Drugs of Today (DRUGS TODAY) (Spain) 1996, 32/SUPPL. I (7-21)
CODEN: MDACA ISSN: 0025-7656
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 60

Modafinil, which is presently used in the treatment of narcolepsy, induces EEG arousal in mammals, including rhesus monkeys and produces behavioral arousal in mice and rats without the induction of stereo-typed behaviors. Pharmacological analysis suggests an indirect involvement of central alphainf 1-adrenergic mechanisms but not of dopamine systems in the behavioral activating action of modafinil. Studies on the neurochemical mechanisms of the vigilance promoting actions of modafinil show no or only weak effects on brain monamides. It is of interest that modafinil can increase glutamine synthase mRNA and protein in various brain regions, suggesting an activation of astrocyte metabolism through wakefulness produced by modafinil and leading to energy production. The major neurochemical action of modafinil, however, appears to be a reduction of GABA release in several brain regions, such as the cerebral cortex and the nucleus accumbens, which is dependent upon 5-HT receptor activation. Increases of dopamine release in the rat nucleus accumbens appears to involve the inactivation of a local GABAergic mechanism. It is postulated that a reduction of GABA release plays a relevant role in the wakefulness produced by modafinil, especially in view of the strong inhibitory regulation by GABA of the excitatory glutamate pathways.

11/3,AB/60 (Item 5 from file: 72)
DIALOG(R)File 72:EMBASE

06470566 EMBASE No: 1996130042
Relative vulnerability of dopamine and GABA neurons in mesencephalic culture to inhibition of succinate dehydrogenase by malonate and 3- nitropropionic acid and protection by NMDA receptor blockade

Zeevalk G.D.; Derr-Yellin E.; Nicklas W.J.
Department of Neurology, UMDNJ-Robert Wood Johnson Med. Sch., 675 Hoes Lane,Piscataway, NJ 08854 United States

Journal of Pharmacology and Experimental Therapeutics (J. PHARMACOL. EXP. THER.) (United States) 1995, 275/3 (1124-1130)
CODEN: JPETA ISSN: 0022-3565
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The effects of different severities of metabolic stress on dopamine (DA) and gamma-aminobutyric acid (GABA) cell loss were examined in rat mesencephalic culture. Partial metabolic inhibition was induced in 12-day-old cultures by a 24-hr treatment with various concentrations of 3-nitropropionic acid(3-NPA, 0.1-0.5 mM) or malonate (10-50 mM), irreversible and reversible inhibitors of the Krebs cycle enzyme, succinate dehydrogenase. Cell damage to the DA and GABA populations was assessed after a 48-hr recovery period by simultaneous measurement of high affinity uptake for sup 3H-DA and sup 1sup 4C-GABA.. 3-NPA or malonate caused a dose-dependent loss of DA uptake (EC$D5inf 0 0.21 or 42 mM, respectively). 3-NPA treatment was equally detrimental to the GABA population, whereas malonate exposure did not cause any significant loss of GABA uptake. The presence of the NMDA antagonist, MK-801 (1 muM), during 24 hr of 3-NPA or malonate treatment fully protected against DA and GABA loss with 50 mM malonate or 0.25 mM 3-NPA and partially protected versus 0.5 mM 3- NPA. To determine the degree of metabolic stress imposed by 3-NPA and malonate, 12-day-old cultures were treated with 0.5 mM 3-NPA or 50 mM malonate for 3 hr and the rate of lactate formation was measured. Lactate was increased nearly 2-fold at 3 hr of treatment with 3-NPA, but was not significantly elevated above basal with malonate treatment. SDH activity was decreased by 48 or 58% after 3 hr of treatment with 0.25 and 0.5 mM 3-NPA, respectively. 3-NPA (0.5 mM) did not produce an increase in extracellular glutamate after 3 hr of exposure. However, this length of exposure to 3-NPA was sufficient to result in an 84% reduction in DA uptake measured after 48 hr of recovery. Consistent with malonate producing a much milder metabolic stress, a 3-hr exposure to 50 mM malonate did not result in significant toxicity when assayed after 48 hr of recovery. These studies indicate that DA neurons in vitro display a relative vulnerability to mild metabolic stress as compared with mesencephalic GABAergic neurons, which results in toxicity that is mediated by NMDA receptors. NMDA receptor involvement was not correlated with a rise in extracellular glutamate during partial metabolic inhibition and further suggests that under these conditions, factors other than increased extracellular glutamate may be responsible for NMDA receptor activation.

11/3,AB/61 (Item 1 from file: 442)
DIALOG(R)File 442:AMA Journals

00113293

Attenuation of the Neuropsychiatric Effects of Ketamine With Lamotrigine Support for Hyperglutamatergic Effects of N-methyl-D-aspartate Receptor

Antagonists (AR[redacted]LE)

ANAND, AMIT; CHARNEY, DENNIS S.; OREN, DAN A.; BERMAN, ROBERT M.; HU, X. SYLVIA; CAPPIELLO, ANGELA; KRYSTAL, JOHN H.
Archives of General Psychiatry
Mar, 2000; Original Article: tzy270
LINE COUNT: 00642

Background: The cognitive, behavioral, and mood effects of N-methyl-D-aspartate (NMDA) receptor antagonists, such as phencyclidine and ketamine, have been used to study the effects of NMDA receptor dysfunction. Pharmacological modulation of the effects of NMDA receptor antagonists, such as ketamine, may lead to development of novel therapeutic agents for psychiatric illnesses such as schizophrenia. Preclinical studies indicate that some ketamine effects may be mediated through increased glutamate release. In this study, we tested the hypothesis that lamotrigine, a drug reported to inhibit glutamate release, will reduce the neuropsychiatric effects of ketamine in humans. Method: Healthy subjects (n = 16) completed 4 test days involving the administration of lamotrigine, 300 mg by mouth, or placebo 2 hours prior to administration of ketamine (0.26 mg/kg by intravenous bolus and 0.65 mg/kg per hour by intravenous infusion) or placebo in a randomized order under double-blind conditions. Behavioral and cognitive assessments were performed at baseline and after administration of the medications. Results: Lamotrigine significantly decreased ketamine-induced perceptual abnormalities as assessed by the Clinician-Administered Dissociative States Scale (P<.001); positive symptoms of schizophrenia as assessed by the Brief Psychiatric Rating Scale positive symptoms subscale (P<.001); negative symptoms as assessed by the Brief Psychiatric Rating Scale negative symptoms subscale (P<.05); and learning and memory impairment as assessed by the Hopkins Verbal Learning Test (P<.05). However, lamotrigine increased the immediate mood-elevating effects of ketamine (P<.05). Conclusions: Glutamate release-inhibiting drugs may reduce the hyperglutamatergic consequences of NMDA receptor dysfunction implicated in the pathophysiologic processes of neuropsychiatric illnesses such as schizophrenia. Further study is needed.
Arch Gen Psychiatry. 2000;57:270-276

11/3,AB/62 (Item 2 from file: 442)
DIALOG(R)File 442:AMA Journals

00111032

A New Twist for Stopping the Shakes? Revisiting GABAergic Therapy for Essential Tremor (ARTICLE)

LOUIS, ELAN D.
Archives of Neurology
July, 1999; Special Article: tzn807
LINE COUNT: 00196

Aside from physiological tremor, essential tremor (ET) is by far the most common cause of tremor in humans, affecting large numbers of individuals in every human population.1/ The crude prevalence of ET has been conservatively estimated to be between 0.4% and 3.9%, although some estimates of the prevalence of ET among the elderly are higher than 20%.1/ Essential tremor is the most prevalent adult-onset movement disorder, and is also regarded as one of the most common neurological disorders of adults, with a prevalence that is similar to or greater than that of stroke, Alzheimer disease, migraine headache, and lumbosacral pain syndromes.2/ Essential tremor is as much as 20 times more prevalent than Parkinson disease.3/

11/3,AB/63 (Item 3 from file: 442)
DIALOG(R)File 442:AMA Journals

00110507

Parkinson Disease, the Effect of Levodopa, and the ELLDOPA Trial (ARTICLE)

FAHN, STANLEY
Archives of Neurology
MAY, 1999; Neurotherapeutics: tzn529
LINE COUNT: 00764

The introduction of effective doses of levodopa for the treatment of Parkinson disease (PD)1,2/ was a revolutionary step in overcoming symptoms of a progressive neurodegenerative disease. This took place a little more than 30 years ago, and still, today, levodopa remains the most effective drug for the reversal of symptoms of PD.1,2/ If there were no associated adverse effects with long-term use, treatment of PD would be a simple matter. But most of the physician's effort in providing optimum care of patients with PD is in trying to overcome all too common adverse effects of levodopa.

11/3,AB/64 (Item 4 from file: 442)
DIALOG(R)File 442:AMA Journals

00110309

A Randomized Placebo-Controlled Comparative Trial of Gabapentin and Propranolol in Essential Tremor (ARTICLE)

GIRONELL, ALEXANDRE; KULISEVSKY, JAIME; BARBANOJ, MANEL; LOPEZ-VILLEGAS, DOLORES; HERNANDEZ, GONZALO; PASCUAL-SEDANO, BERTA
Archives of Neurology
Apr, 1999; Original Contribution: tzn475
LINE COUNT: 00535

Background: New medication is needed to treat essential tremor. Preliminary evidence suggests that gabapentin may be effective in the treatment of this disorder. Objective: To study the effects of gabapentin in a comparative, double-blind, crossover, placebo-controlled trial of patients who have essential tremor. Patients and Methods: 16 patients with essential tremor (6 with a new onset and 10 with a 2-week washout period of previous treatment with propranolol hydrochloride) received gabapentin (Neurontin), 400 mg 3 times daily; propranolol hydrochloride, 40 mg 3 times daily; and placebo for 15 days with a 1-week washout period between treatments. Major Outcome Measures: Major outcome evaluations consisted of a Tremor Clinical Rating Scale, accelerometric recordings, and a self-reported disability scale obtained before drug intake on study days 1 and 15 of each treatment period. In addition, the initial (day 1) and superimposed (day 15) drug effects were studied before and 2, 4, 6, and 8 hours after drug intake. Results: At day 15, both gabapentin and propranolol demonstrated significant and comparable efficacy in reducing tremor from baseline in all tremor measures. The initial drug effects evaluated through accelerometry revealed no significant changes with the use of a placebo, but gabapentin and propranolol use significantly reduced tremor power. Conclusion: Gabapentin may be useful for the treatment of essential tremor. Arch Neurol. 1999;56:475-480

11/3,AB/65 (Item 5 from file: 442)
DIALOG(R)File 442:AMA Journals

00110226

Transcranial Magnetic Stimulation Applications in Neuropsychiatry (ARTICLE)

GEORGE, MARK S.; LISANBY, SARAH H.; SACKEIM, HAROLD A.
Archives of General Psychiatry
Apr, 1999; News and Views: tzy300
LINE COUNT: 01302

In the 1990s, it is difficult to open a newspaper or watch television and not find someone claiming that magnets promote healing. Rarely do these claims stem from double-blind, peer-reviewed studies, making it difficult to separate the wheat from the chaff. The current fads resemble those at the end of the last century, when many were falsely touting the benefits of direct electrical and weak magnetic stimulation. Yet in the midst of this popular interest in magnetic therapy, a new neuroscience field has developed that uses powerful magnetic fields to alter brain activity--transcranial magnetic stimulation. This review examines the basic principles underlying transcranial magnetic stimulation, and describes how it differs from electrical stimulation or other uses of magnets. Initial studies in this field are critically summarized, particularly as they pertain to the pathophysiology and treatment of neuropsychiatric disorders. Transcranial magnetic stimulation is a promising new research and, perhaps, therapeutic tool, but more work remains before it can be fully integrated in psychiatry's diagnostic and therapeutic armamentarium.
Arch Gen Psychiatry. 1999;56:300-311

11/3,AB/66 (Item 6 from file: 442)
DIALOG(R)File 442:AMA Journals

00107992

Pharmacological Therapy in Progressive Supranuclear Palsy (ARTICLE)

KOMPOLITI, K.; GOETZ, C. G.; LITVAN, IRENE; JELLINGER, K.; VERNY, M.
Archives of Neurology
Aug, 1998; Original: tzn1099
LINE COUNT: 00308

Background: To our knowledge, previous reports on drug treatment in progressive supranuclear palsy have not evaluated autopsy-confirmed cases. Objective: To evaluate pharmacological treatment responses from detailed clinical records in patients with autopsy-confirmed progressive supranuclear palsy. Subjects and Methods: We reviewed medical records for clinical presentation and pharmacological response in 12 patients with autopsy-confirmed progressive supranuclear palsy diagnosed using the National Institute of Neurological Disorders and Stroke pathologic criteria. For each drug class, exposure, global positive response, and specific positive response (parkinsonism, other movement disorders, or gaze dysfunction) were recorded. Results: Drug classes examined were dopaminergics (all patients), tricyclics (3 patients), methysergide maleate (3 patients), 5-hydroxytryptophan (2 patients), and anticholinergics and selective serotonin inhibitors (1 patient). Positive clinical response was detected in 7 of the patients receiving dopaminergic drugs and in 1 patient each receiving tricyclics, methysergide, and

5-hydroxytryptophan, respectively. None of the patients responded markedly however, and there was no persistent beneficial effect. Use of dopaminergic drugs most frequently improved parkinsonian features, but disabling adverse effects included orthostatic hypotension (6 patients), hallucinations and delusions (3 patients), gastrointestinal complaints (3 patients), and dizziness (1 patient). Only 1 patient developed dyskinesia. Conclusion: Use of antiparkinsonian medications and other neurotransmitter replacement therapies was largely ineffective and caused frequent adverse effects in this series of patients with autopsy-confirmed with progressive supranuclear palsy. Arch Neurol. 1998;55:1099-1102

11/3,AB/67 (Item 7 from file: 442)
DIALOG(R)File 442:AMA Journals

00105063

`Vascular Depression' Hypothesis (ARTICLE)

ALEXOPOULOS, GEORGE S.; MEYERS, BARNETT S.; YOUNG, ROBERT C.; CAMPBELL, SCOTT; SILBERSWEIG, DAVID; CHARLSON, MARY
Archives of General Psychiatry
Oct, 1997; News and Views: tzy915
LINE COUNT: 01027

We propose that cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes. The `vascular depression' hypothesis is supported by the comorbidity of depression,vascular disease, and vascular risk factors and the association of ischemic lesions to distinctive behavioral symptoms. Disruption of prefrontal systems or their modulating pathways by single lesions or by an accumulation of lesions exceeding a threshold are hypothesized to be central mechanisms in vascular depression. The vascular depression concept can generate studies of clinical and heuristic value. Drugs used for the prevention and treatment of cerebrovasculardisease may be shown to reduce the risk for vascular depression or improve its outcomes. The choice of antidepressants in vascular depression may depend on their effect on neurologic recovery from ischemic lesions. Research can clarify the pathways to vascular depression by focusing on the site of the lesion, the resultant braindysfunction, the presentation of depression and time of onset, and the contribution of nonbiological factors. Arch Gen Psychiatry. 1997;54:915-922

11/3,AB/68 (Item 8 from file: 442)
DIALOG(R)File 442:AMA Journals

00101862

Reduced Blue Cone Electroretinogram in Cocaine-Withdrawn Patients (ARTICLE)

ROY, MONIQUE; ROY, ALEC; WILLIAMS, JOHN; WEINBERGER, LAWRENCE; SMELSON, DAVID
Archives of General Psychiatry
Feb, 1997; Original Article: tzy153
LINE COUNT: 00300

Background: The main reinforcing effect of cocaine is alteration of dopaminergic neurotransmission in the brain reward systems. Since dopamine is found in high concentrations in the retina, we investigated whether cocaine dependence may be associated with abnormalities of the

electroretinog[redacted] Methods: We compa[redacted] recently withdrawn cocaine-dependent patients (n=20) with age-, se[redacted], and race-matched normal subjects (n=20) for responses of cone photoreceptors to light flashes on full-field electroretinograms.Results: Cocaine-dependent patients had significantly reduced blue cone electroretinogram responses compared with matched normal subjects. Conclusions: This result suggests that cocaine-withdrawn patients have a dysregulation of blue cone function. The electroretinogram maybe useful in future studies of cocaine-dependent patients. Arch Gen Psychiatry. 1997;54:153-156

11/3,AB/69 (Item 9 from file: 442)
DIALOG(R)File 442:AMA Journals

00092714

Fluctuating Parkinson's Disease Treatment With the Long-Acting Dopamine Agonist Cabergoline (ARTICLE)

AHLSKOG, J. ERIC; MUENTER, MANFRED D.; MARAGANORE, DEMETRIUS M.; MATSUMOTO, JOSEPH Y.; LIEBERMAN, ABRAHAM; WRIGHT, KATHY F.; WHEELER, KAY
Archives of Neurology
Dec, 1994; Original: tzn1236
LINE COUNT: 00516

Objective: Assessment of the very long-acting dopamine agonist medication cabergoline in the control of motor fluctuations in Parkinson's disease. Design: Open-label trial (13 weeks). Setting: Referral centers (Mayo Clinic, Rochester, Minn, and Scottsdale, Ariz). Patients: Volunteer sample of 41 patients with idiopathic Parkinson's disease who were experiencing motor fluctuations while receiving stable doses of carbidopa and levodopa. Intervention: Adjunctive oral cabergoline was incrementally administered once daily with the maintenance dose determined by the clinical response (maximum dose, 5 mg/d). Main Outcome Measures: Standardized serial motor examinations were performed, beginning anywhere from 30 minutes before and continuing to 6 hours after test doses of medications were administered. Scores during adjunctive cabergoline therapy were compared with the prestudybaseline scores during therapy with carbidopa and levodopa without cabergoline. Results: Adjunctive cabergoline therapy significantly improved meanmotor scores at the time of each standardized serial examination, from 30 minutes to 6 hours after the administration of test doses of medications. Significant motor score improvement was also measured 24hours after the last cabergoline dose was administered, suggesting a very long-acting antiparkinsonian effect. Mean dyskinesia scores wereslightly but nonsignificantly elevated. Diary card `off-time' was improved by 42%, whereas the levodopa dosage was reduced by 18%. Onlythree patients dropped out (7% of the total), which contrasts with much higher dropout rates owing to adverse events in previous clinical trials of other antiparkinsonian dopamine agonists. Conclusions: Cabergoline improved motor control in patients with Parkinson's disease who were experiencing clinical fluctuations. Possible advantages of this medication include an extended clinical response (persisting to 24 hours), tolerability, and ease of use (once per day administration). (Arch Neurol. 1994;51:1236-1241)

11/3,AB/70 (Item 10 from file: 442)
DIALOG(R)File 442:AMA Journals

00092504

Regional Cerebral Blood Flow in Mood Disorders, III Treatment and Clinical Respo (ARTICLE)

NOBLER, MITCHELL S.; SACKEIM, HAROLD A.; PROHOVNIK, ISAK; MOELLER, JAMES R.; MUKHERJEE, SUKDEB; SCHNUR, DAVID B.; PRUDIC, JOAN; DEVANAND, D. P.
Archives of General Psychiatry
Nov, 1994; Original Article: ps_884
LINE COUNT: 01247

Background: Global and regional deficits in cerebral blood flow and glucose metabolism have been reported in major depression, but there is limited information on the effects of somatic treatment and clinical recovery on these abnormalities. Methods: We assessed cortical blood flow with the xenon 133 technique in depressed patients prior to a course of electroconvulsive therapy (ECT), 30 minutes before and 50 minutes after a single treatment, and during the week following ECT. Acute (preictal and postictal) effects of a single treatment also were studied in manic patients. Results: In the depressed and manic groups, larger blood flow reductions in the acute period, both globally and in particular patterns of brain regions, were associated with a superior clinical outcome following the treatment course. In depressed patients, similar patterns were observed for the blood flow changes over a fulltreatment course. Blood flow reductions in anterior cortical regions were strongly associated with a positive clinical response in both depression and mania. Conclusions: The findings indicated that cerebral blood flow abnormalities in major depression were not reversed by successful treatment with ECT. Rather, particularly in responders, ECT resulted in additional perfusion reductions. The therapeutic properties of ECTare related to reduced functional brain activity in specific neural regions. (Arch Gen Psychiatry. 1994;51:884-897)

11/3,AB/71 (Item 11 from file: 442)
DIALOG(R)File 442:AMA Journals

00090472

Stiff-Man Syndrome Report of a Case (ARTICLE)

Archives of Internal Medicine
June 13,, 1994; Clinical Observation: im_1285
LINE COUNT: 00326

Stiff-man syndrome is a well-described, but rare and often overlooked, neuromuscular syndrome of rigidity, spasm, and gait abnormality that is associated with several endocrinologic and autoimmune disorders. A patient exhibiting many typical features of stiff-man syndrome had intermittent symptoms for 22 years before the correct diagnosis was made. Similar to many described patients, she was diabetic, hyperthyroid, and had elevated islet cell, antithyroid,and glutamic acid decarboxylase antibody levels. The high frequency of diabetes mellitus among patients with stiff-man syndrome is emphasized, as is increasing evidence to suggest that elaboration of anti-glutamic acid decarboxylase and anti-islet cell antibodies may play a role in the pathophysiologic state of the disorder. (Arch Intern Med. 1994;154:1285-1288)

11/3,AB/72 (Item 12 from file: 442)
DIALOG(R)File 442:AMA Journals

00087670

A Primer of Current Molecular Genetic Strategies for Clinicians (ARTICLE)

HOOPER, PLEASANT F.
Archives of Otolaryngology
oct, 1993; State of the Art: p1085
LINE COUNT: 01019

For the clinician to take full advantage of the rapid advances in molecular medicine, a working knowledge of the recombinant DNA methodologies employed will be required. This primer introduces current cloning strategies by examination of the cloning of the cystic fibrosis gene, an opioid receptor, and olfactory receptors that used the methodologies of DNA linkage analysis, functional cloning, and polymerase chain reaction with degenerate oligonucleotide primers, respectively. Molecular information obtainedafter cloning has had immediate effects on diagnosis and genetic counseling and holds the promise of novel treatment strategies, including somatic gene therapy. (Arch Otolaryngol Head Neck Surg. 1993;119:1085-1094)

11/3,AB/73 (Item 13 from file: 442)
DIALOG(R)File 442:AMA Journals

00085060

Toward a Neuroanatomy of Obsessive-Compulsive Disorder (ARTICLE)

INSEL, THOMAS R.
Archives of General Psychiatry
September, 1992; Comment: p739
LINE COUNT: 00618

11/3,AB/74 (Item 14 from file: 442)
DIALOG(R)File 442:AMA Journals

00055026

Oxygen Radicals and Neuropsychiatric Illness: Some Speculations (Article)

Lohr, James B., MD
Archives of General Psychiatry
1991; 48: 1097 (10)

Free radicals are reactive chemical species with an unpaired electron that are produced through a variety of physiologic and pathologic processes. Free radicals have been implicated in a variety of neuropsychiatric conditions, many of which are marked by the gradual development of psychopathologic symptoms and movement disorder. There is evidence that radical-induced damage may be important in Parkinson's disease, tardive dyskinesia, metal intoxication syndromes, and Down's syndrome, and possibly also in schizophrenia, Huntington's disease, and Alzheimer's disease. Although some of this evidence is highly speculative, it may offer an avenue for further understanding and treatment of these conditions.

11/3,AB/75 (Item 15 from file: 442)
DIALOG(R)File 442:AMA Journals

00055014

Exiitotoxicity and Dopaminergic Dysfunction in the Acquired Immunodeficiency Syndrome Dementia Complex; Therapeutic Implications (Article)

Kieburts, Karl D., MD; Epstein, Leon Gary, MD; Gelbard, Harris A., MD; Greenamyre, J. Timothy, MD, PhD
Archives of Neurology
1991; 48: 1281 (4)

Human immunodeficiency virus infection is frequently complicated by a syndrome of central nervous system dysfunction known as the acquired immunodeficiency syndrome dementia compolex (ADC). The ADC is characterized by abnormalities in cognition, motor performance, and behavior, and it produces serious morbidity in a significant number of patients with acquired immunodeficiency syndrome. The pathogenesis of ADC is unclear, but appears to be caused by the human immunodeficiency virus itself, rather than by a secondary opportunistic process. Herein, we review the data regarding the pathogenesis of ADC and phypothesize a mechanism involving excitotoxicity and dopaminergic dysfunction. N-methyl-D-aspartate receptor antagonists may be of therapeutic benefit, as these agents may both limit glutamate-mediated neuronal dysfunction and improve dopaminergic neuronal function.

11/3,AB/76 (Item 16 from file: 442)

00051891

Allelic Association of the D.sub.2 Dopamine Receptor Gene With Receptor-Binding Characteristics in Alcoholism (Article)

Noble, Ernest P., PhD, MD; Blum, Kenneth, PhD; Ritchie, Terry, PhD; Montgomery, Anne, MSc; Sheridan, Peter J., PhD
ARCHIVES of General Psychiatry
1991; 48: 648 (7)

The allelic association of the human \D.sub.2 dopamine receptor gene with the binding characteristics of the \D.sub.2 dopamine receptor was determined in 66 brains of alcoholic and nonalcoholic subjects. In a blinded experiment, DNA from the cerebral cortex was treated with the restriction endonuclease Taql and probed with a 1.5-kilobase (kb) digest of a clone (\lambda\hD2G1) of the human \D.sub.2 dopamine receptor gene. The binding characteristics (\K.sub.d \binding affinity and \B.sub.max \number of binding sites\) of the \D.sub.2 dopamine receptor were determined in the caudate nuclei of these brains using tritiated spiperone as the ligand. The adjusted \K.sub.d was significantly lower in alcoholic than in nonalcoholic subjects. In subjects with the A1 allele, in whom a high association with alcoholism was found, the \B.sub.max was significantly reduced compared with the \B.sub.max of subjects with the A2 allele. Moreover, a progressively reduced \B.sub.max was found in subjects with A2/A2, and A1/A2, and A1/A1 alleles, with subjects with A2/A2 having the highest mean values, and subjects with A1/A1, the lowest. The polymorphic pattern of the \D.sub.2 dopamine receptor gene and its differential expression of receptors suggests the involvement of the dopaminergic system in conferring susceptibility to at least one subtype of severe alcoholism.

11/3,AB/77 (Item 17 from file: 442)

00045300

Clonidine Treatment of Alzheimer's Disease (ORIGINAL CONTRIBUTION)

MOHR, ERICH; SCHLEGEL, JERRY; FABBRINI, GIOVANNI; WILLIAMS, JILL; MOURADIAN, M. MARAL; MANN, ULRIKE M.; CLAUS, JULES J.; FEDIO, PAUL; CHASE, THOMAS N.
Archives of Neurology
April, 1989 ; 46: 376-378
LINE COUNT: 00118 WORD COUNT: 01630

ABSTRACT: A loss of cortical noradrenergic innervation may contribute to the intellectual deterioration in Alzheimer's disease. To test the hypothesis that noradrenergic replacement may confer symptomatic benefit, a double-blind, placebo-controlled therapeutic trial with clonidine hydrochloride (Catapres), a centrally active noradrenergic receptor agonist, was undertaken in eight patients with the clinical diagnosis of Alzheimer's disease. No statistically significant changes in cognitive function were found over a range of doses, including those that produced clinically observable side effects. These preliminary results indicate a need for alternative noradrenergic replacement strategies in Alzheimer's disease.

11/3,AB/78 (Item 18 from file: 442)

00041923

Alzheimer's Disease; Aminergic-Cholinergic Alterations in Hypothalamus (ORIGINAL CONTRIBUTIONS)

SPARKS, D. LARRY; DEKOSKY, STEVEN T.; MARKESBERY, WILLIAM R.
Archives of Neurology
September, 1988; 45: 994-999
LINE COUNT: 00336 WORD COUNT: 04650

ABSTRACT: To better understand the role of the hypothalamus in Alzheimer's disease (AD), we have measured dopamine, norepinephrine (NE), and serotonin (5HT) levels, tritiated spiperone and tritiated serotonin blinding, and choline acetyltransferease (ChAT) and acetylcholinesterase activity in seven subregions of the hypothalamus from 18 normal control subjects and ten patients with AD. We have found a significant reduction of 5HT in the anterior hypothalamus, lateral hypothalamus, and posterior lateral hypothalamus and a decline in spiperone binding in the anterior hypothalamus of patients with AD. The ChAT activity was found to be diminished only in the posterior lateral hypothalamus of patients with AD. No NE or dopamine alterations were found in any region of the AD hypothalamus. In the normal hypothalamus, dopamine, NE, and 5HT were found to be regionally distributed. Our study documents region-specific neurotransmitter abnormalities in the AD hypothalamus and raises the question of the relationship of these changes, especially in 5HT, to some of the noncognitive clinical alterations observed in AD.

11/3,AB/79 (Item 19 from file: 442)

00041713

Cerebrospinal [redacted]luid Amino Compounds in [redacted]kinson's Disease; Alterations due to Carbidopa/Levodopa (ORIGINAL [redacted]NTRIBUTION)

MANYAM, BALA V.; FERRARO, THOMAS N.; HARE, THEODORE A.
Archives of Neurology
January, 1988 ; 45: 48-50
LINE COUNT: 00182 WORD COUNT: 02522

ABSTRACT: Employing a triple-column ionexchange/fluorometric procedure, 29 amino compounds, including amino acid neurotransmitters, were measured in lumbar cerebrospinal fluid (CSF) from two groups of patients with idiopathic Parkinson's disease de novo (n = 6) and those who were treated with carbidopa/levodopa (n = 6), and from neurologically normal controls (n = 10). Consideration was given to in vivo and in vitro factors known to influence levels of various CSF constituents. Results showed statistically significant decreases in the levels of gamma-aminobutyric acid, homocarnosine, phosphoethanolamine, and threonine, and elevation of ornithine levels, in the CSF of de novo patients with Parkinson 's disease compared with controls. These changes "normalized" following treatment with carbidopa/levodopa. This study suggests that Parkinson's disease may be characterized by defects in specific amino compound metabolic pathways, resulting in central nervous system amino compound imbalances that may contribute to the pathophysiology of this disorder. Carbidopa/levodopa thereapy tends to "normalize" these amino compound imbalances.

11/3,AB/80 (Item 20 from file: 442)
DIALOG(R)File 442:AMA Journals

00031899

Pharmacologic Probe With Progabide of GABA Mechanisms in Essential Tremor (ORIGINAL CONTRIBUTION)

KOLLER, WILLIAM C.; RUBINO, FRANK; GUPTA, SUDHA
Archives of Neurology
September, 1987; 44: 905-906
LINE COUNT: 00100 WORD COUNT: 01389

ABSTRACT: Progabide, a gamma-aminobutyric acid agonist, was given to ten patients with essential tremor in a double-blind, placebo-controlled crossover study. The effect of progabide did not differ from that of placebo. Alterations in gamma-aminobutyric acid neurotransmission do not appear to be involved in the pathogenesis of essential tremor.

11/3,AB/81 (Item 21 from file: 442)
DIALOG(R)File 442:AMA Journals

00031070

Cerebral Lateralization; Biological Mechanisms, Associations, and Pathology: I. A Hypothesis and a Program for Research (SPECIAL ARTICLE)

GESCHWIND, NORMAN
Archives of Neurology
May, 1985; 42: 428-459
LINE COUNT: 02391 WORD COUNT: 33009

11/3,AB/82 (Item 22 from file: 442)
DIALOG(R)File 442:AMA Journals
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00030886
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Low CSF gamma-Aminobutyric Acid Levels in Parkinson's Disease; Effect of Levodopa and Carbidopa (ORIGINAL CONTRIBUTIONS)

MANYAM, BALA V.
Archives of Neurology
July, 1982; 39: 391-392
LINE COUNT: 00111 WORD COUNT: 01541

ABSTRACT: Levels of gamma-aminobutyric acid (GABA) in CSF were measured in patients with Parkinson 's disease (n = 14) and sex-matched controls (n = 14). One patient underwent a spinal tap before and after treatment. The mean (+/- SD) CSF GABA levels were 200 +/- 70 pmole/mL in controls and 121 +/- 52 pmole/mL in patients with Parkinson's disease. In the untreated patients with Parkinson's disease, the CSF GABA level was 95 +/- 31 pmole/mL (n = 7) and in those who were treated with levodopa and carbidopa the level was 144 +/- 53 pmole/mL (n = 8). No significant difference was seen in plasma GABA levels between the controls and patients with Parkinson's disease. The decreased GABA level in CSF, which was elevated by levodopa, supports the concept that in Parkinson's disease, the GABA-dopamine interaction in the substantia nigra may be an important compensatory mechanism counteracting the dopamine neuronal loss. (Arch Neurol 1982;39:391-392)

11/3,AB/83 (Item 23 from file: 442)
DIALOG(R)File 442:AMA Journals
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00030592
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Bilateral Internuclear Ophthalmoplegia Reversed by Naloxone (BRIEF COMMUNICATIONS)

RIZZO, MATTHEW
Archives of Neurology
April, 1983; 40: 242-243
LINE COUNT: 00090 WORD COUNT: 01253

ABSTRACT: We encountered an apparent bilateral internuclear ophthalmoplegia (INO) in a stuporous patient who used narcotics and benzodiazepines and had taken phenytoin sodium for drug-withdrawal seizures. The INO was promptly reversed by administration of the narcotic antagonist naloxone, which binds opiate receptors. This suggests the INO resulted from a specific toxic effect of narcotics, but opiate receptors have not been anatomically demonstrate within the medial longitudinal fasciculus or associated structures. Stimulation of inhibotory GABA -ergic (alpha-aminobutyric acid) vestibulo-ocular fibers may have been related to INO in this case. (Arch Neurol 1983;40:242-243)

11/3,AB/84 (Item 24 from file: 442)
DIALOG(R)File 442:AMA Journals
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00030197
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Cerebellar Norepinephrine in Patients With Parkinson's Disease and Control Subjects (ORIGINAL CONTRIBUTION)

KISH, STEPHEN J.; SHANNAK, KATHLEEN S.; RAJPUT, ALI H.; GILBERT, JOSEPH J.; HORNYKIEWICZ, OLEH
Archives of Neurology
June, 1984 ; 41: 612-614
LINE COUNT: 00171 WORD COUNT: 02365

ABSTRACT: Norepinephrine was measured in postmortem cerebellar cortex of 22 non-neurological control subjects and nine patients with Parkinson 's disease, using the high-performance liquid chromatography method with amperometric detection.In all control subjects, substantial amounts of norepinephrine were found in cerebellar cortex. There was a moderate negative correlation between age of control subjects and cerebellar norepinephrine concentration. In the patients with Parkinson 's disease, the cerebellar cortical norepinephrine levels were significantly below normal. This is in accord with previously reported reduced norepinephrine levels in locus ceruleus and other regions of the parkinsonian brain. Although the main symptoms of Parkinson's disease are primarily caused by disturbed basal ganglia (dopamine) function, cerebellar dysfunction related to norepinephrine may contribute to some abnormalities of motor performance in this disorder. (Arch Neurol 1984; 41: 612-614)

11/3,AB/85 (Item 25 from file: 442)
DIALOG(R)File 442:AMA Journals

00026795

Occurrence of Myoclonus in Patients Treated With Cyclic Antidepressants (ORIGINAL ARTICLE)

GARVEY, MICHAEL J.
Archives of General Psychiatry
March, 1987; 44: 269-272
LINE COUNT: 00229 WORD COUNT: 03170

ABSTRACT: Myoclonus associated with cyclic antidepressant therapy has been considered to be a rare phenomenon. Ninety-eight patients who were to begin receiving cyclic antidepressant therapy were prospectively evaluated for myoclonus. Thirty patients experienced clincially insignificant drug-associated myoclonus. Nine patients had clinically significant myoclonus. The myoclonus was reversible with the discontinuation of therapy but tended to persist if medication changes were not made. None of the tested clinical variables were able to predict which patients would develop myoclonus.

11/3,AB/86 (Item 26 from file: 442)
DIALOG(R)File 442:AMA Journals

00026730

Imaging of Neurotransmitter Receptors in the Living Human Brain (PERSPECTIVE)

SEDVALL, GORAN; FARDE, LARS; PERSSON, ANDERS; WIESEL, FRISTS-AXEL
Archives of General Psychiatry

October, 198[redacted] 43: 995-1005
LINE COUNT: [redacted]91 WORD COUNT: 08167

11/3,AB/87 (Item 27 from file: 442)
DIALOG(R)File 442:AMA Journals

00026634

Long-term Pimozide Pretreatment Differentially Affects Behavioral Responses to Dextroamphetamine in Schizophrenia; Further Exploration of the Dopamine Hypothesis of Schizophrenia (ORIGINAL ARTICLES)

VAN KAMMEN, DANIEL P.; DOCHERTY, JOHN P.; MARDER, STEPHEN R.; RAYNER, JUDITH N.; BUNNEY, WILLIAM E.
Archives of General Psychiatry
March, 1982; 39: 275-281
LINE COUNT: 00350 WORD COUNT: 04839

ABSTRACT: In ten of 30 schizophrenic patients treated with pimozide for five weeks, 20 mg of dextroamphetamine sulfate induced an increase in psychosis. The number of patients becoming more psychotic with the dextroamphetamine challenge was not significantly different from the number who worsened after dextroamphetamine challenge when pretreated with placebo. Half of the patients who showed a psychotic response to dextroamphetamine during placebo pretreatment responded to dextroamphetamine with an increase in psychosis after pimozide treatment . Dextroamphetamine induced a worsening in patients who had improved with pimozide. The stability of the preinfusion condition is more important to the type of response to dextroamphetamine than long-term pretreatment with a dopamine receptor blocker. The activation-euphoria response to dextroamphetamine was unaffected by pimozide pretreatment, which suggests that the changes in psychosis and activation may be regulated by different mechanisms. These findings question the postulated relationship between the antipsychotic drug response and dopamine receptor blockade.

11/3,AB/88 (Item 28 from file: 442)
DIALOG(R)File 442:AMA Journals

00026277

The Effect of Tetrahydroisoxazolopyridinol (THIP) in Tarvide Dyskinesia; A New gamma-Aminobutyric Acid Agonist (ORIGINAL ARTICLES)

KORSGAARD, SOREN; CASEY, DANIEL E.; GERLACH, JES; HETMAR, OLE; KALDAN, BJORN; MIKKELSEN, LEIF B.
Archives of General Psychiatry
September, 1982; 39: 1017-1021
LINE COUNT: 00275 WORD COUNT: 03797

ABSTRACT: Gamma-Aminobutyric acid (GABA) agonists have been proposed for the treatment of tardive dyskinesia, but their therapeutic potential has been limited by side effects and toxicity. To elucidate further the role of GABA in neuroleptic-induced dyskinesias, we evaluated tetrahydroisoxazolopyridinol (THIP), a new, less toxic GABA analog and GABA receptor agonist, in both a dose-finding (single-dose) pilot study with five patients and a longer (four-week) placebo-controlled study with 13 patients. The patients were videotaped during a standardized examination; tardive dyskinesia,

parkinsonian [redacted]toms, and eye-blinking rates [redacted]e rated blindly and randomly. The maximal short-term dose of THIP [redacted]s 10 to 25 mg, whereas in the longer-term study the highest daily dose ranged from 20 to 120 mg. Tardive dyskinesia was unchanged during THIP treatment , but preexisting parkinsonism increased significantly and eye-blinking rates decreased. Psychiatric symptoms showed no significant changes, although tension and depression lessened. Side effects included sedation, confusion, dizziness, vomiting, and myoclonic jerks. Although THIP is not an effective new treatment for tardive dyskinesia, more specific GABA agonist should be evaluated in future studies of this syndrome.

3/3,AB/34 (Item [redacted] from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04259449 82089930 PMID: 7316490
Regional activities of metabolic enzymes and glutamate decarboxylase in human brain.
Maker HS; Weiss C; Weissbarth S; Silides DJ; Whetsell W
Annals of neurology (UNITED STATES) Oct 1981, 10 (4) p377-83, ISSN 0364-5134 Journal Code: 6AE
Contract/Grant No.: NS-05184, NS, NINDS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Interpretation of biochemical measurements in the human brain after death is complicated by a variety of premortem, perimortem, and postmortem factors. The activity of glutamic acid decarboxylase (**GAD**) in particular has been found to vary considerably among human brains. In contrast to neurotransmitter-associated enzymes, metabolic enzymes are present in all brain cells and should not be specifically lost by patterned neuronal cell loss such as that which occurs in **Parkinson** disease. We compared the activity of **GAD** to that of the metabolic enzymes creatine kinase (CK), adenylate kinase, hexokinase, beta-glucuronidase, and malate, lactate, glucose-6-phosphate, and isocitrate dehydrogenases in 24 regions of six human brains. Of the metabolic enzymes, only CK showed a 5-fold variation approaching that of **GAD**. Like **GAD**, CK activity was stable postmortem, but its activity was apparently inversely related to the severity and duration of the preterminal illness. CK may be a useful marker of agonal deterioration.

3/3,AB/35 (Item 35 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04006223 83163228 PMID: 6131932
Striatal GABAergic neuronal activity is not reduced in **Parkinson**'s disease.
Perry TL; Javoy-Agid F; Agid Y; Fibiger HC
Journal of neurochemistry (UNITED STATES) Apr 1983, 40 (4) p1120-3, ISSN 0022-3042 Journal Code: JAV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The content of gamma-aminobutyric acid (GABA) and the activities of glutamic acid decarboxylase (**GAD**) and tyrosine hydroxylase (TH) were measured in whole putamen obtained at autopsy from 13 patients dying with idiopathic **Parkinson** 's disease and 13 appropriate control subjects. Mean GABA content was significantly elevated (by 28%) in the putamen of the **Parkinson**'s disease patients. TH activity was markedly reduced, while there was no significant reduction of **GAD** activity in the putamen of these patients. GABA content was also measured in both sides of the striatum in rats which had received unilateral injections of 6-hydroxydopamine (6-OHDA) in the vicinity of the axons of the nigrostriatal projection. Mean GABA content was found significantly elevated (by 33%) in the ipsilateral striatum. Loss of dopaminergic nigrostriatal neurons, in both human **Parkinson**'s disease and in the rat 6-OHDA model, is accompanied by increased striatal GABA content. The assumption that GABAergic neurotransmission is reduced in the striatum in **Parkinson**'s disease may not be correct.

3/3,AB/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

03979991 83064304 PMID: 6292818

Pharmacodynamic effects and possible therapeutic uses of THIP, a specific GABA-agonist.
Christensen AV; Svendsen O; Krogsgaard-Larsen P
Pharmaceutisch weekblad. Scientific edition (NETHERLANDS) Oct 22 1982, 4 (5) p145-53, ISSN 0167-6555 Journal Code: OZW
Languages: ENGLISH
Document type: Journal Article; Review
Record type: Completed
THIP (4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol) is a potent and specific GABA receptor agonist which does not influence the GABA uptake system or GABA metabolizing enzymes. The specificity for the GABA receptor is also demonstrated by lack of action on monoaminergic, cholinergic, histaminergic or opiate receptors. Since in recent years GABA receptor stimulants-among others THIP--have become available many have speculated as to what clinical indication GABA-ergic stimulation might be an important element. The first suggestion was that GABA-ergic drugs by an inhibitory effect on the dopamine neurons would improve the antischizophrenic effect of neuroleptics and improve tardive dyskinesia. Furthermore, studies on brains of deceased **Parkinson** and Huntington's chorea patients have demonstrated a low level of GABA and its synthesizing enzyme glutamic acid decarboxylase (**GAD**) in the basal ganglia. Also in epilepsy and diseases with dementia a deficit in the GABA system has been proposed. Therefore a therapeutic strategy for these diseases may be supplementary treatment with drugs which increase GABA receptor activity. Furthermore, recent results in humans have shown that GABA agonists perhaps also could be of benefit in mania and depressions. When considering the neurophysiological elements of nociception and muscle tone it is also reasonable to suggest that GABA-ergic stimulation may reduce pain perception and muscle tone.

3/3,AB/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

03513354 79045236 PMID: 152197
Neurochemical findings in Huntington's chorea.
Bird ED; Iversen LL
Essays in neurochemistry and neuropharmacology (ENGLAND) 1977, 1 p177-95, ISSN 0147-0205 Journal Code: EMI
Languages: ENGLISH
Document type: Journal Article; Review
Record type: Completed
Huntington's chorea is a dominantly inherited disorder that usually leads to involuntary movements in the third or fourth decade. On gross pathological examination of the post-mortem brain there is a marked atrophy of the caudate nucleus and putamen. Histological examination reveals cell loss in most regions of the brain, although the hippocampus is usually remarkably free of any abnormalities. Studies to detect a biochemical defect in patients with chorea have been largely unrewarding. Since chorea appears to be the clinical counterpart of **Parkinson**'s disease a number of investigations on dopamine metabolism have been carried out by measuring dopamine in the post-mortem choreic brain, and HVA, a metabolite of dopamine, in the CSF of patients. Most studies have found the dopamine concentrations to be normal or sometimes decreased and the activity of the biosynthetic enzyme for dopamine, tyrosine hydroxylase, is normal. The discovery that the inhibitory neurotransmitter, GABA, and the biosynthetic enzyme **GAD** are greatly decreased in the post-mortem choreic brain provides some rational explanation for the uncontrolled movements in this disorder. The other significant abnormality found in many, but not all, choreic post-mortem brains has been a decrease in the biosynthetic enzyme for acetylcholine, choline acetyl transferase. The evidence that GABA receptors are intact in choreic brain provides an added stimulus for the development of useful GABA-mimetic drugs. For the ultimate eradication of this distressing disorder, however, a search must continue for the primary defect in order that this can be detected before the onset of symptoms, or

hopefully in amniotic fluid.

3/3,AB/38 (Item 38 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

03505387 78047583 PMID: 144789
Neurotransmitter enzyme abnormalities in senile dementia. Choline acetyltransferase and glutamic acid decarboxylase activities in necropsy brain tissue.
Perry EK; Gibson PH; Blessed G; Perry RH; Tomlinson BE
Journal of the neurological sciences (NETHERLANDS) Nov 1977, 34 (2) p247-65, ISSN 0022-510X Journal Code: JBJ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Reductions in 2 neurotransmitter synthesizing enzymes in brain, glutamic acid decarboxylase (**GAD**) and choline acetyltransferase (CAT), have been found in dementias of different origins, including senile dementia (Alzheimer type). Significant reductions in cerebral **GAD** have also been found in depression (unipolar). The **GAD** reductions did not generally appear to be localised in any specific region of the brain examined. However, the reduction of CAT in the hippocampus, relative to reductions in other areas examined, was substantially greater in the brains with Alzheimer-type changes. **GAD** and CAT activities in normal brains were examined for the effects of some variable factors inherent in necropsy biochemical measurements. These factors included: (i) age; (ii) agonal status; (iii) time of death, and (iv) delay in tissue sampling; and **GAD** was found to be significantly influenced by (ii), (iii) and (iv) and CAT by (i), (iii) and (iv). None of these factors accounted for the total alterations in the enzyme activities of the mentally abnormal brains. The results indicate that reductions in cerebral **GAD** require to be interpreted with caution in view of the sensitivity of this enzyme to premortem status but that reductions in cerebral CAT may be a more reliable index of pathological change in senile (Alzheimer-type) dementia.

3/3,AB/39 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13374922 BIOSIS NO.: 200200003743
Genetically engineered GABA-producing neurons shorten the duration and raise the threshold of hippocampal afterdischarges.
AUTHOR: Thompson K W(a); Wasterlain C G(a); Tobin A J
AUTHOR ADDRESS: (a)Neurology, VHAWLA/UCLA, Los Angeles, CA**USA
JOURNAL: Society for Neuroscience Abstracts 27 (2):p2347 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Transplantation of genetically engineered cells can be used to deliver therapeutic molecules to the brain. Diseases such as epilepsy and **Parkinson**'s disease are potentially treatable with this technology. We have previously reported that cells genetically engineered to express the GABA synthesizing enzyme **GAD65** make and release GABA. These cells can modify behavioral seizures when transplanted into the substantia nigra or the hippocampus. Here we report the acute electrographic effects of cells transplanted into the hippocampus. Rats were stereotaxically transplanted with conditionally immortalized mouse cortical neurons that were engineered with **GAD65** or beta-galactosidase. After 150K cells were transplanted bilaterally, an

electrode was inserted into the left hippocampus adjacent to the cells for stimulating and recording electrographic seizures. One week to ten days later the animals were stimulated daily with a 1 sec train of a 60Hz stimulus repeated in ascending 20uA steps until a seizure was recorded. The electrographic responses were stored and later analyzed using DataWave software. The animals receiving GABA-producing cells had shorter afterdischarge durations compared to control from the beginning of the experiment. Interestingly, the afterdischarge threshold was not different on the first day of stimulation but was dramatically different the next day and stayed high thereafter. These data provide evidence that localized electrographic seizures can be manipulated by genetically engineered cells and they suggest that some effects might be activity dependent.

2001

3/3,AB/40 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13355883 BIOSIS NO.: 200100563032
GFRalpha-1 mRNA in dopaminergic and nondopaminergic neurons in the substantia nigra and ventral tegmental area.
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AUTHOR ADDRESS: (a)Cellular Neurophysiology, National Institute on Drug Abuse, 5500 Nathan Shock Drive, Baltimore, MD, 21224: mmorales@intra.nida.nih.gov**USA
JOURNAL: Journal of Comparative Neurology 441 (2):p106-117 December 10, 2001
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LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Glial cell line-derived neurotrophic factor (GDNF) is a survival factor for several types of neurons, including dopaminergic (DAergic) neurons. GDNF binds with high affinity to the GDNF family receptor alpha-1 (GFRalpha-1), which is highly expressed in the midbrain. Using anatomical and lesion techniques, we demonstrated that GFRalpha-1 was expressed in DAergic and non-DAergic neurons in the rat midbrain. Immunohistochemical characterization of GFRalpha-1-expressing neurons indicated that most of the neurons that were immunopositive for the DAergic marker tyrosine hydroxylase (TH) expressed GFRalpha-1 in the substantia nigra pars compacta (SNC). In contrast, fewer TH-containing neurons expressed GFRalpha-1 in the substantia nigra pars reticulata (SNR) and the ventral tegmental area (VTA). Depletion of GFRalpha-1/TH neurons was observed in the SNC following treatment with the neurotoxin 6-hydroxydopamine (6-OHDA); however, GFRalpha-1 expression remained in some neurons located in the SNR. The gamma-aminobutyric acid (GABA)ergic nature of GFRalpha-1-expressing neurons located in the SNR, which were resistant to (6-hydroxydopamine) 6-OHDA, was established by their expression of glutamic acid decarboxylase (**GAD**; the synthesizing enzyme for GABA). Further analysis indicated that coexpression of GFRalpha-1 and **GAD** varied in a rostrocaudal gradient in the SNR, substantia nigra pars lateralis (SNL), and VTA. Midbrain DAergic and GABAergic neurons have been previously classified according to their Ca2+ binding protein (CaBP) content; thus, we also sought to investigate the proportion of midbrain. GFRalpha-1-expressing neurons containing parvalbumin (PV), calbindin (CB), and calretinin (CR) in the midbrain. Although GFRalpha-1 expression was found mainly in CB- and CR-immunoreactive neurons, it was rarely observed in PV-immunolabeled neurons. Analysis of the proportion of GFRalpha-1-expressing neurons for

each CaBP subpopulation indicated the coexistence of GFRalpha-1 with CR in the VTA and all [redacted] divisions of the SN; double-la[redacted]ed GFRalpha-1/CR neurons were distributed in the SNC, SNR, SNL, and VTA. GFRalpha-1/CB neurons were also detected in the SNC, SNL, and VTA. Expression of GFRalpha-1 in DAergic and non-DAergic neurons in the rat SN and VTA suggests that GDNF, via GFRalpha-1, might modulate DAergic and GABAergic functions in the nigrostriatal, mesolimbic, and nigrothalamic circuits of the adult rat.

2001

3/3,AB/41 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13325975 BIOSIS NO.: 200100533124
Effects of thalamic denervation on glutamate decarboxylase and cytochrome oxidase subunit I mRNA expression in the rat basal ganglia.
AUTHOR: Bacci J J(a); Kerkerian-Le Goff L(a); Bosler O; Salin P(a)
AUTHOR ADDRESS: (a)Lab. Cellular and Functional Neurobiology, CNRS, Marseille**France
JOURNAL: Society for Neuroscience Abstracts 27 (1):p1357 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
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RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: This study examined the consequences of ibotenate-induced unilateral lesion of intralaminar thalamic nuclei on mRNA expression of cytochrome oxidase subunit I (CoI) and/or of the two glutamate decarboxylase isoforms, **GAD65** and **GAD67**, in the basal ganglia structures by in situ hybridization histochemistry. In the striatum, **GAD67** mRNA levels decreased rostrally at 5 and 12 days post-lesion (about -30%), whereas **GAD65** was down-regulated caudally at 12 days (-29%), in the lesion side. In the subthalamic nucleus, CoI mRNA levels decreased ipsilaterally at 5 days (-31%) and bilaterally at 12 days (-46% ipsi and -27% contralateral). In the globus pallidus, both **GAD67** and **GAD65** mRNA levels decreased ipsilaterally at 5 and 12 days (-20% to -36%). In the entopeduncular nucleus, selective bilateral decreases in **GAD67** mRNA expression were found at 5 and 12 days (about -50% and -40%). Conversely, in the substantia nigra pars reticulata, only **GAD65** mRNA expression was reduced bilaterally at both time point. These data show that the thalamus exerts a widespread excitatory influence onto the basal ganglia network which cannot be accounted for only by its known direct connections. Given the recent data showing that intralaminar thalamic nuclei are a major non dopaminergic site of neurodegeneration in **Parkinson**'s disease, these results may have critical bearing for understanding the cellular basis of basal ganglia dysfunction in **parkinsonism**. We are now investigating the effects of combined thalamic lesion and dopamine denervation in the basal ganglia.

2001

3/3,AB/42 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13325969 BIOSIS NO.: 200100533118
Alterations on **GAD67** mRNA in basal ganglia nuclei following repeated

administration of L-DOPA and the adenosine A2A receptor antagonist SCH58261.
AUTHOR: Carta A R(a); Pinna A(a); Morelli M(a)
AUTHOR ADDRESS: (a)Dept Toxicol, Univ of Cagliari, Cagliari**Italy
JOURNAL: Society for Neuroscience Abstracts 27 (1):p1355 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: In the 6-hydroxydopamine (6-OHDA) model of **Parkinson**'s disease, chronic administration of L-DOPA, but not SCH58261+L-DOPA, induces alterations in behavioural response that are predictive of dyskinesia. In this study we evaluated postsynaptic changes in different structures of basal ganglia in 6-OHDA lesioned rats treated for 19 days with either L-DOPA (6 or 3 mg/kg), or SCH58261 (5 mg/kg) plus L-DOPA (3 mg/kg). In situ hybridization was performed to assess **GAD67** mRNA levels as a marker of GABAergic neurons activity in the striatum, globus pallidus and substantia nigra. **GAD67** mRNA was increased in the striatum and globus pallidus but not in the substantia nigra ipsilateral to the 6-OHDA lesion, with respect to the unlesioned side. Chronic treatment with 6 mg/kg of L-DOPA further increased **GAD67** mRNA levels in both the striatum and globus pallidus, whereas dramatically reduced **GAD67** mRNA in the substantia nigra. Neither SCH58261 in association with the low dose of L-DOPA, nor L-DOPA alone (3 mg/kg) significantly affected **GAD67** mRNA in the striatum and substantia nigra. In the globus pallidus **GAD67** mRNA was modestly increased by these treatments. The results suggest that an excessive inhibition of substantia nigra neurons, secondary to an increase of GABA activity in the globus pallidus, may underlie L-DOPA induced dyskinesia. By contrast, blockade of A2A receptors associated with a low dose of L-DOPA produces less marked changes of **GAD67** activity in the basal ganglia structures analysed, which could explain the lack of dyskinetic responses, and points to A2A receptors antagonists as a usefull approch in **Parkinson**'s disease.

2001

3/3,AB/43 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13325510 BIOSIS NO.: 200100532659
The mRNA for the long isoform of GABAA receptor gamma2 subunit increases in the subthalamic nucleus after nigrostriatal lesions.
AUTHOR: Liang X(a); Mehta A(a); Chesselet M F(a)
AUTHOR ADDRESS: (a)Neurology, UCLA, Los Angeles, CA**USA
JOURNAL: Society for Neuroscience Abstracts 27 (1):p1146 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The increased activity of subthalamic nucleus (STN) neurons plays a critical role in **Parkinson**'s disease. The STN receives GABAergic inputs from the globus pallidus (GPe) and expresses GABAA receptors. Nigrostriatal lesions result in decreased spontaneous activity but increased burst firing and expression of **GAD67** mRNA in Gpe,

suggesting that GABA release may be increased in the STN. Behavioral studies from our laboratory have shown a decreased response to GABA A agonists in the STN after nigrostriatal lesions. We have now explored the molecular mechanisms of GABA A receptor alterations in the STN by measuring the mRNAs encoding alpha1, beta2 and gamma2 subunits with real-time quantitative RT-PCR in rats 21 days after ipsilateral 6-OHDA lesions of the nigrostriatal pathway. The STN of 8 lesioned and 8 control rats were punched at -20*C and pooled for each group for RNA extraction. Dopamine depletion was confirmed behaviorally in all lesioned rats. Minor (10-15%) differences were detected for the alpha1, beta2 and gamma2S subunit mRNAs, however a robust increase (+118%) in gamma2L mRNA was observed in the STN of lesioned rats. Since gamma2L contains an additional phosphorylation site for protein kinase C, increased expression of gamma2L may indicate an increased phosphorylation of the receptor. Phosphorylation negatively modulates GABAA receptors by reducing the amplitude of GABA-activated currents. Thus the results suggest a molecular mechanism that may mediate the decreased response to GABA agonists in the STN and contribute to the change in activity of the STN in **Parkinson**'s disease.

2001

3/3,AB/44 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13292622 BIOSIS NO.: 200100499771
Novel functions of ubiquitin C-terminal hydrolase and therapeutic trial.
AUTHOR: Takizawa S(a); Wang Y L(a); Osaka H(a); Yuda K(a); Sakurai M(a); Aoki S(a); Nishikawa K(a); Satoh Y(a); Wada E(a); Harada T(a); Harada C (a); Takada K; Takeda A; Wada K(a)
AUTHOR ADDRESS: (a)Department of Degenerative Neurological Diseases, National Institute of Neuroscience, NCNP, Kodaira**Japan
JOURNAL: Society for Neuroscience Abstracts 27 (1):p517 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Functional loss of ubiquitin carboxy terminal hydrolase 1 (UCH-L1) leads to gracile axonal dystrophy (**gad**) in mouse. Human mutation, Ile92Met, is reported in one **Parkinson**'s disease family. Although UCH-L1 comprises up to apprx1 percentage of cellular proteins in the brain, substrates/interacting proteins and in vivo functions are yet to be identified. We have tried to capture substrates by using anti-ubiquitin antibody coupled column and mutant UCH-L1 column that lacks the catalytic activity. For interacting proteins, we took affinity purification using anti-UCH-L1 antibody column. After two-dimensional electrophoresis, candidate's spots were analyzed for peptide mapping and micro-sequencing. Both cytosolic and nuclear proteins were identified, suggesting various and novel functions of UCH-L1. As a relatively small (apprx23 kd) cytosolic protein, UCH-L1 becomes a good target for protein introduction therapy. HIV-TAT derived eleven amino acids were attached to the N-terminus of UCH-L1 as a fusion protein. TAT-UCH-L1 was successfully introduced into dopamin producing SH-SY5Y cells. The therapeutic trial for the correction of **gad** phenotype by TAT-UCH-L1 is ongoing.

2001

3/3,AB/45 (Item 7 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

13290328 BIOSIS NO.: 200100497477
GAPDH antisense oligonucleotide protects dopaminergic neuronal death occurring with exposure of the cerebrospinal fluid from PD patients.
AUTHOR: Fukuhara Y(a); Takeshima T(a); Kashiwaya Y(a); Mishima K(a); Ishitani R; Nakashima K(a)
AUTHOR ADDRESS: (a)Neurology, Tottori Univ, Yonago**Japan
JOURNAL: Society for Neuroscience Abstracts 27 (1):p527 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Cerebrospinal fluid (CSF) from patients with **Parkinson**'s disease (PD) have been reported to contain factors toxic to mesencephalic dopaminergic neurons (MDNs). In this study, we explored the possible involvement of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in the death of MDNs induced by exposure of <10kDa fraction of CSF from PD patients. Specimens of CSF were obtained from 5 patients with de novo PD without any medication and 4 control patients with other neurological diseases. Primary rat mesencephalic microisland cultures were treated with 10muM GAPDH sense or antisense oligonucleotides at 4th days in vitro (DIV4), and 2 hours later, exposed to 10% of <10kDa fraction of CSF from PD, from other patients or 10% (v/v) PBS as control. Survivals of MDNs were evaluated at DIV6 by double immunostaining of tyrosine hydroxylase (TH) and microtubule associated protein-2 (MAP2). Overexpression of GAPDH was detected by using anti-GAPDH antibody. CSF from PD patients, but not the control patients, selectively decreased the survival of TH+ neurons (46.4+-5.1% of control). GAPDH antisense oligonucleotides remarkably rescued MDNs from the toxicity of CSF (up to 80.3+-7.2% of control). Further, GAPDH overexpression was observed in dying TH+ neurons. These results suggest the imvolvememt of GAPDH in the degeneration of MDNs in PD, and its possibility as a therapeutic target of PD.

2001

3/3,AB/46 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13290309 BIOSIS NO.: 200100497458
High frequency stimulation of the subthalamic nucleus: Selective effects on dopamine denervation-induced cellular defects in the output structures of the basal ganglia in the rat.
AUTHOR: Salin P P(a); Forni C(a); Manrique C(a); Kerkerian-Le Goff L(a)
AUTHOR ADDRESS: (a)Lab. Cellular and Functional Neurobiology, CNRS, Marseille**France
JOURNAL: Society for Neuroscience Abstracts 27 (1):p523 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
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RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: High frequency stimulation (HFS) of the subthalamic nucleus (STN) is now recognized as an effective treatment for advanced **Parkinson** 's disease. However, the impact of STN HFS on the changes in gene

expression resulting from dopamine denervation in the basal ganglia structures remains unknown. This study examined the effects of STN HFS in intact and hemiparkinsonian freely moving rats on mRNA levels of enkephalin and substance P in the striatum and of glutamate decarboxylase (**GAD67**) in the globus pallidus (GPe), entopeduncular nucleus (EP) and substantia nigra pars reticulata (SNr) by in situ hybridization histochemistry. Animals were killed after 2 hours of HFS at a frequency of 130Hz, the intensity being adjusted individually at the threshold value inducing dyskinetic movement of the contralateral forepaw. No significant effect of STN HFS was measured in intact animals. In hemiparkinsonian rats, the dopamine lesion-induced changes in intraneuronal **GAD67** mRNA levels were reversed by STN HFS in the SNr, partially antagonized in the EP but unaffected in the GPe. STN HFS did not affect the lesion-mediated overexpression of enkephalin mRNA nor the decrease in substance P in the striatum. These data question the current view that GPe reactivity to dopamine lesion be mediated through STN dysfunction and suggest that STN HFS may act, at least at short term, by antagonizing the overactivity of the basal ganglia output structures, directly, rather than through circuits involving striatal or GPe neurons.

2001

3/3,AB/47 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13290299 BIOSIS NO.: 200100497448
Engineered GABA-releasing cells suppress tremor in an animal model of **parkinsonism**.
AUTHOR: Carlson B(a); Behrstock S; Tobin A; Salamone J(a)
AUTHOR ADDRESS: (a)Univ Connecticut, Storrs, CT**USA
JOURNAL: Society for Neuroscience Abstracts 27 (1):p521 2001
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CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Research in **Parkinson**'s disease (PD) has focused upon functions of striatal dopamine. The vast majority of striatal efferents are GABAergic. Medial globus pallidus (MGP) and substantia nigra pars reticulata (SNr) are the basal ganglia output areas that are targets of these projections. Research from animal models has shown that stimulation of GABA receptors in these areas can produce motor effects that are antitremorogenic. Tremulous jaw movements (TJM) in rats have been used as a model of PD tremor. Recent studies have demonstrated that stimulating GABA receptors in SNr can suppress TJM and local blockade GABA receptors in SNr induces TJM. In addition to pharmacotherapies, transplantation techniques have been employed as treatments for neurodegenerative diseases and with PD most of this work has focused upon transplantation of DA cells into striatum. In view of recent evidence indicating that stimulation of GABA receptors in SNr could produce antiparkinsonian effect in animal models the present study employed the TJM model in rats to study the feasibility of transplanting engineered GABA-releasing cells to alleviate symptoms of PD. To achieve conditional-immortalization the oncogene was the temperature-sensitive mutated allele of the SV40 large Tag. Cells expressed **GAD**-65 or beta-gal. Two days post-surgery all rats received IP injections of 4mg/kg pilocarpine to induce TJM. Implantation of **GAD** cells increased SNr GABA and reduced TJM. This effect was blocked by bicuculline and enhanced by GABA transport inhibitors. The present results suggest that implantation of GABA cells into SNr, or MGP, or STN provides an alternative transplantation strategy

for the treatment of PD.

2001

3/3,AB/48 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13288583 BIOSIS NO.: 200100495732
GAD65 transduction of the subthalamic nucleus changes the action of excitatory projections to the substantia nigra.
AUTHOR: Oshinsky M L(a); Luo J; During M J
AUTHOR ADDRESS: (a)Neurology, Thomas Jefferson University, Philadelphia, PA **USA
JOURNAL: Society for Neuroscience Abstracts 27 (1):p521 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The subthalamic nucleus (STN) has a prominent excitatory connection with the substantia nigra (SN). In **Parkinson**'s disease (PD), overactivity in the STN leads to progressive degeneration of dopamine neurons in the SN, as well as the common features of **Parkinsonism** such as tremor, rigidity and bradykinesia. We hypothesize that changing the excitatory projection from the STN to the SN into an inhibitory projection, using a gene therapy approach, will alleviate the symptoms of PD. We performed extracellular electrophysiology and microdialysis in the SN of normal rats and rats treated with the recombined associate adenovirus (rAAV) containing the gene for human glutamic acid decarboxylase 65 (rAAV CBA-hGAD65), which converts glutamate to GABA in neurons. The medial forebrain bundle was lesioned after the virus was injected into the STN to model PD. Extracellular recordings of the SN during STN stimulation in normal rats (n=4) revealed 78% (n=14/19 neurons) excitatory responses, 5% (n=1/19) inhibitory, and 21% (n=4/19) had no response. In **GAD** transduced rats (n=5), we found 17% (n=3/18 neurons) excitatory responses, 78% (n=14/18) inhibitory and 5% (n=1/18) had no response. Microdialysis experiments detected a 4.4X increase in mean GABA concentration in the SN of **GAD** transduced rats (n=4) during low frequency (10Hz, 5') electrical stimulation of the STN, compared to a 1.5X increase in control rats (n=3). These experiments demonstrate that **GAD** transduction of neurons in the STN increases inhibition in the SN and decreases the excitatory effect of STN stimulation on neurons in the SN which may alleviate the symptoms of PD.

2001

3/3,AB/49 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13284898 BIOSIS NO.: 200100492047
Ubiquitin C-terminal hydrolase as a regulator of ubiquitin level.
AUTHOR: Osaka H(a); Wang Y L(a); Takizawa S(a); Aoki S(a); Sakurai M(a); Li H(a); Hara Y(a); Takada K; Noda M; Wada K(a)
AUTHOR ADDRESS: (a)Department of Degenerative Neurological Diseases, National Institute of Neuroscience, NCNP, Kodaira**Japan
JOURNAL: Society for Neuroscience Abstracts 27 (1):p517 2001
MEDIUM: print

CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience
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RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Ubiquitin carboxy terminal hydrolase 1 (UCH-L1) is abundant protein in the nervous system and testis. An in-frame deletion including exons 7 and 8 of Uchl1 was found to be the cause of gracile axonal dystrophy (**gad**) mouse that exhibit spinal and cerebellum neurodegeneration. One large pedigree of **Parkinsons** disease co-segregated with Isoleucine to Methionine mutation at the vicinity to the catalytic center (I92M) of UCH-L1. In **gad** mouse, UCH-L1 protein was below detectable level with immuno-blotting and immuno-histochemical analysis. Mutant UCH-L1 encoded by **gad** allele which lacks 42 amino acids, was produced with transfection into E. coli and subsequent gel purification. The activity to hydrolyze ubiquitin C-terminus of ubiquitin-AMC was not detected. Moreover, the deleted legion in the **gad** mouse was proposed to correspond to a core domain. Thus, UCH-L1 was concluded to be functionally lost in the **gad** mouse. The free ubiquitin level of the cerebrum, cerebellum, and medulla oblongata were reduced in the **gad** mouse from the birth. The production of free ubiquitin, following various stresses, were significantly reduced in the **gad** mouse. Thus, UCH-L1 regulates free ubiquitin level and affect protein ubiqutination in the central nervous system.

2001

3/3,AB/50 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13271015 BIOSIS NO.: 200100478164
Differential distribution of alpha-, beta- and gamma-synucleins with special reference to different neuronal components.
AUTHOR: Li J Y(a); Dahlstrom A(a)
AUTHOR ADDRESS: (a)Dept of Anat and Cell Biol, Univ. Gothenburg, Gothenburg **Sweden
JOURNAL: Society for Neuroscience Abstracts 27 (1):p254 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience
San Diego, California, USA November 10-15, 2001
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RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Recent evidence showed that alpha-synuclein (Syn) is a major component of Lewy bodies in idiopathic **Parkinson**'s disease. In the present study, we have studied the detailed distribution of alpha-, beta- and gamma-Syns in the CNS with double/triple immuno-stainings combined with a confocal microscope. In the relationship between the three Syn family, alpha-Syn and beta-Syn were highly co-localized with each other in the cortex, hippocampus, striatum, and the spinal cord, however, alpha-Syn was virtually absent from the gamma-Syn containing nerve terminals. Colocalization study with different specific tissue markers demonstrated that alpha-Syn and tyrosine hydroxylase (TH) partially co-localized in the CNS; that beta-Syn was exclusive from TH containing structures and that gamma-Syn highly colocalized with TH. In contrast, alpha-Syn was absent from the structures containing vesicular acetylcholine transporter (VAChT), while beta- and gamma-Syns appeared highly co-existed with VAChT. Furthermore, alpha- and beta-Syns virtually exclusive from peptidergic (CGRP) terminals, while gamma-Syn showed a

high colocalization. Finally, alpha-Syn was completely colocalized with GABAergic (**GAD** positive) terminals in striatum and substantial nigra. The present study revealed that alpha-Syn is predominantly present in catecholaminergic, GABAergic neurons; that beta-Syn was prominent in cholinergic neurons and that gamma-Syn widely present in catecholaminergic, cholinergic, peptidergic (CGRP) neurons. The differential localization among the Syn family members indicates their possible functional predominance in different type of neurons.

2001

3/3,AB/51 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13064804 BIOSIS NO.: 200100271953
Effects of 8-OH-DPAT, a 5-HT1A receptor agonist, on L-DOPA-induced motor complications in 6-OHDA-lesioned rats.
AUTHOR: Kimura Tamaki(a); Tomiyama Masahiko(a); Tanaka Hiroyasu(a); Maeda Tetsuya(a); Yamato Hirosi(a); Kannari Kazuya(a); Matsunaga Muneo(a)
AUTHOR ADDRESS: (a)Dept of Neurol Sci, Inst of Brain Sci, Hirosaki Univ Sch of Med, Hirosaki**Japan
JOURNAL: Neuroscience Research Supplement (24):pS122 2000
MEDIUM: print
CONFERENCE/MEETING: 23rd Annual Meeting of the Japan Neuroscience Society and the 10th Annual Meeting of the Japanese Neural Network Society Yokohama, Japan September 04-06, 2000
ISSN: 0921-8696
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

3/3,AB/52 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12902092 BIOSIS NO.: 200100109241
Apoptosis in **Parkinson**'s disease--**GADPH** nuclear accumulation, increased caspase 3 and Bax immunoreactivity in the nigra.
AUTHOR: Tatton N A(a)
AUTHOR ADDRESS: (a)Mt. Sinai Sch Med/NYU, New York, NY**USA
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-66720 2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: There is a lack of consensus as to whether apoptosis contributes to neuronal death in **Parkinson**'s disease (PD). In situ end labeling (ISEL) also known as the TUNEL method, when used to detect DNA strand breaks in the PD nigra has provided conflicting results. ISEL used alone cannot distinguish between apoptotic or necrotic DNA strand breaks, therefore we developed a double-labeling method which combines ISEL with the cyanine dye YOYO-1 to visualize apoptotic chromatin condensation. Because ISEL/YOYO identifies the final,degradative stage of apoptosis, it was necessary to use immunocytochemistry on alternate sections to determine which effector molecules may participate in the death process

in PD. Nigral paraffin and cryosections were obtained from 10 clinically and neuropathologically identified cases of PD and 6 age-matched controls. Increased numbers of joint, ISEL/YOYO positive, apoptotic nuclei were identified in the PD nigra compared with controls. Increased Bax and caspase 3 immunoreactivity was found in melanized neurons in the PD nigra (antiserum specific for the activated fragment of caspase 3) compared to age-matched controls. Many of the Lewy bodies in the PD nigra were GAPDH (glyceraldehyde-3-phosphate dehydrogenase) immunopositive. Importantly,GAPDH nuclear accumulation (which has been used as an apoptotic indicator in vitro) was also observed in melanized neurons in the PD nigra. These data suggest that melanized, dopaminergic neurons die via a mitochondrially-dependent pathway in PD

2000

3/3,AB/53 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12901865 BIOSIS NO.: 200100109014
Strategies to identify genes accounting for ATP-dependent iron transport.
AUTHOR: Baranano D E(a); Snyder S H; Ferris C D
AUTHOR ADDRESS: (a)Johns Hopkins Sch Med, Baltimore, MD**USA
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-62512 2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
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LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Iron overload contributes to the pathophysiology of several neurologic diseases, including Alzheimer's disease and **Parkinson**'s disease. While the roles of transferrin and ferritin in cellular iron uptake and storage are well known, the molecular basis for cellular iron mobilization/release remains obscure. Recently, we found that heme oxygenases (HO1 and HO2) reduce cellular iron levels and protect cells from stress-induced cell death. We have identified an Fe-ATPase activity functionally coupled to heme oxygenases. It appears that the iron, released from heme by HO, is extruded from cells by the Fe-ATPase. The Fe-ATPase activity is highest in the spleen where the vast majority of heme degradation occurs. In addition, it is highly induced both in vivo and in cell culture by excess heme or iron. This induction is dependent on both transcription and translation, suggesting that subtractive library screening could lead to the identification of the gene or genes that account for this activity. Using PCR-based cDNA enrichment, we have constructed two subtracted libraries derived from tissue or cells in which the Fe-ATPase is enriched at least eight-fold. Our first library is constructed from a macrophage cell line grown in iron-enriched media. Cells grown in normal media are used as the "driver." The HO1 is present in high amounts in this cDNA, confirming enrichment for iron-induced genes. Furthmore, the common housekeeping gene GAPDH was depleted from the enriched cDNA. Pharmacologic studies of the Fe-ATPase activity suggest that the enzyme may be a P-type ATPase. We screened our library with degenerate oligonucleotide probes designed to a highly conserved motiff, DKTGT, common to all P-type ATPases. We identified a single band, specific to the subtracted cDNA and neither the unsubtracted or the reverse -subtracted cDNA. A second library was made from spleen, using the kidney as the "driver." This library also has a candidate band when probed with the same degenerate oligonucleotide. We have inserted the two enriched cDNAs into vectors and are screening with degenerate

oligonucleotides and cDNA from the iron-induced condition.

2000

3/3,AB/54 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12880585 BIOSIS NO.: 200100087734
Effects of 8-OH-DPAT, a 5-HT1A receptor agonist, on L-DOPA-induced dyskinesias in rats with nigrostriatal denervation.
AUTHOR: Tomiyama M(a); Kimura T; Tanaka H; Maeda T; Yamato H; Kannari K; Matsunaga M; Mengod G
AUTHOR ADDRESS: (a)Hirosaki Univ. Sch. of Med., Hirosaki**Japan
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-27810 2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: In rats with unilateral 6-OHDA lesions of the nigrostriatal pathway, the motor effects of L-DOPA became enhanced by intermittent administration. It appears that marked fluctuation of dopamine concentrations in the striatum causes such behavioral sensitization, that is regarded as a model of dyskinesias in **Parkinson**'s disease. We have demonstrated that serotonergic neurons play a main role in conversion of L-DOPA and in release of L-DOPA-derived dopamine into the striatum in 6-OHDA rats. In addition, a 5-HT1A receptor agonist, 8-OH-DPAT, reduces L-DOPA-derived dopamine in the striatum of 6-OHDA rats. We hypothesized that coadministration of 8-OH-DPAT with L-DOPA reduced fluctuation of dopamine concentrations in the denervated striatum and improved dyskinesias. Hence, 6-OHDA rats were administrated 8-OH-DPAT (1 mg/kg) with L-DOPA (50 mg/kg) and benserazide (12.5 mg/kg) (DPAT group) or L-DOPA and benserazide (DOPA group) or saline twice a day for 14 days. Behavioral sensitization was observed in DOPA group, however, contralateral rotation after the last treatment was reduced in DPAT group compared to DOPA group. Rats were killed one day after the last injection, and sections through the striatum were processed for in situ hybridization of glutamic acid decarboxylase (**GAD67**) and prodynorphine (PDyn) mRNAs. Expression of **GAD67** and PDyn mRNAs was significantly increased in the denervated striatum of DOPA group, whereas their expression levels were decreased in DPAT group when compared to those of DOPA group. These results suggest that 5-HT1A receptor agonists can improve L-DOPA-induced dyskinesias.

2000

3/3,AB/55 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12874741 BIOSIS NO.: 200100081890
Distribution of **GAD65/GAD67** mRNA in the pallidal complex in normal and **parkinsonian** monkeys relevance for the design of a novel gene-based therapy for **parkinsonism**.
AUTHOR: Wade T V(a); Schneider J S
AUTHOR ADDRESS: (a)Thomas Jefferson Univ., Philadelphia, PA**USA
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-4786

2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The two isoforms of giutamic acid decarboxylase (**GAD65** and **GAD67**), the synthesizing enzymes for GABA, may have different functional roles in regulating basal ganglia output and may have different regional and cellular distributions Since altered pallidal GABAergic activity may underlie motor deficits observed in **parkinsonism**, we have investigated the regional distribution and differential expression of **GAD65** and **GAD67** mRNA at 4 rostrocaudal levels throughout the pallidal complex in normal and **parkinsonian** squirrel monkeys. In normal animals, **GAD65** mRNA was expressed similarly in both internal (GPi) and external (GPe) pallidal segments with no significant rostrocaudal differences in gene expression **GAD67** mRNA was expressed to a greater extent in the GPi than the GPe, with higher levels expressed caudally. In MPTP-treated **parkinsonian** monkeys, **GAD67** mRNA expression was increased in both the GPi and GPe with much larger increases in the GPi especially at more caudal levels. Only minor increases in **GAD65** gene expression were observed in the GPi and gene expression was decreased in the GPe at all rostrocaudal levels. Based on the anatomical distributions of **GAD** isoforms in the pallidum and the assumption that increased activity of GABAergic GPi neurons underlie the expression of **parkinsonian** signs, we performed targeted application of **GAD65** and **GAD67** antisense oligonucleotides to the GPi in an attempt to selectively decrease the abnormal GABAergic activity and to partially ameliorate **parkinsonian** signs. Infusion of **GAD67** antisense into the GPi in 3 **parkinsonian** monkeys caused increased motor activity that was not observed after infusions of a missense sequence or **GAD65** antisense. These results show that regulation of **GAD67** gene expression in the GPi may be critical to the expression of **parkinsonian** motor signs and suggest a potential new treatment strategy for **Parkinson**'s disease.

2000

3/3,AB/56 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12619313 BIOSIS NO.: 200000372815
Differential effect of priming with dopamine agonists on mRNA for **GAD67**, dynorphin and enkephalin in 6OHDA lesioned rats.
AUTHOR: Carta A R(a); Sotgiu A(a); Fenu S(a); Morelli M(a)
AUTHOR ADDRESS: (a)Dept. Toxicology, Cagliari**Italy
JOURNAL: European Journal of Neuroscience 12 (Supplement 11):p135 2000
MEDIUM: print
CONFERENCE/MEETING: Meeting of the Federation of European Neuroscience Societies Brighton, UK June 24-28, 2000
ISSN: 0953-816X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

3/3,AB/57 (Item 19 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)
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12611739 BIOSIS NO.: 200000365241
Distinct electrophysiological phenotype of calbindin-positive dopaminergic midbrain neurons.
AUTHOR: Neuhoff H(a); Neu A(a); Liss B(a); Roeper J(a)
AUTHOR ADDRESS: (a)MRC Anatomical Neuropharmacology Unit, Oxford University, Oxford**UK
JOURNAL: European Journal of Neuroscience 12 (Supplement 11):p216 2000
MEDIUM: print
CONFERENCE/MEETING: Meeting of the Federation of European Neuroscience Societies Brighton, UK June 24-28, 2000
ISSN: 0953-816X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

3/3,AB/58 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

11136825 BIOSIS NO.: 199799757970
Dopaminergic neurons intrinsic to the primate striatum.
AUTHOR: Betarbet Ranjita; Turner Robert; Chockkan Vijay; Delong Mahlon R; Allers Kelly A; Walters Judith; Levey Allan I; Greenamyre J Timothy(a)
AUTHOR ADDRESS: (a)Dep. Neurol., Emory Univ., 1639 Pierce Drive, WMB 6000, Atlanta, GA 30322**USA
JOURNAL: Journal of Neuroscience 17 (17):p6761-6768 1997
ISSN: 0270-6474
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Intrinsic, striatal tyrosine hydroxylase-immunoreactive (TH-i) cells have received little consideration. In this study we have characterized these neurons and their regulatory response to nigrostriatal dopaminergic deafferentation. TH-i cells were observed in the striatum of both control and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys; TH-i cell counts, however, were 3.5-fold higher in the striatum of MPTP-lesioned monkeys. To establish the dopaminergic nature of the TH-i cells, sections were double-labeled with antibodies to dopamine transporter (DAT). Immunofluorescence studies demonstrated that nearly all TH-i cells were double-labeled with DAT, suggesting that they contain the machinery to be functional dopaminergic neurons. Two types of TH-i cells were identified in the striatum: small, aspiny, bipolar cells with varicose dendrites and larger spiny, multipolar cells. The aspiny cells, which were more prevalent, corresponded morphologically to the GABAergic interneurons of the striatum. Double-label immunofluorescence studies using antibodies to TH and glutamate decarboxylase (**GAD**-67), the synthetic enzyme for GABA, showed that 99% of the TH-i cells were **GAD**-67-positive. Very few (lt 1%) of the TH-i cells, however, were immunoreactive for the calcium-binding proteins calbindin and parvalbumin. In summary, these results demonstrate that the dopaminergic cell population of the striatum responds to dopamine denervation by increasing in number, apparently to compensate for loss of extrinsic dopaminergic innervation. Moreover, this population of cells corresponds largely with the intrinsic GABAergic cells of the striatum. This study also suggests that the adult primate striatum does retain some intrinsic capacity to compensate for dopaminergic cell loss.

1997

3/3,AB/59 (Item [redacted] from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10489504 BIOSIS NO.: 199699110649
L-DOPA regulates glutamate decarboxylases mRNA levels in MPTP-treated monkeys.
AUTHOR: Soghomonian Jean-Jacques(a); Pedneault Sophie; Blanchet Pierre J; Goulet Martin; Di Paolo Therese; Bedard Paul J
AUTHOR ADDRESS: (a)Centre de Recherche Neurobiol., Univ. Laval, Hop. Enfant-Jesus, 1401 18e rue, PQ G1J 1Z4**Canada
JOURNAL: Molecular Brain Research 39 (1-2):p237-240 1996
ISSN: 0169-328X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The effect of dopaminergic denervation, alone or followed by chronic intermittent L-DOPA administration, on the levels of mRNAs encoding for the two isoforms of the GABA-synthesizing enzyme, glutamate decarboxylase (**GAD65** and **GAD67**), were measured by in-situ hybridization in the caudate and putamen of macaque monkeys. When compared to control monkeys, the level of **GAD67** mRNA was increased in the putamen and caudate of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys. On the other hand, **GAD65** mRNA labeling in MPTP-treated monkeys was not significantly different from the controls. In MPTP-treated monkeys that received L-DOPA, a significant increase in both **GAD67** and **GAD65** mRNA levels was measured in the putamen when compared to control or MPTP-treated monkeys. The results suggest that the dyskinetic effect of L-DOPA is paralleled by an increased GABAergic activity in the striatum.

1996

3/3,AB/60 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09925166 BIOSIS NO.: 199598380084
Effects of Nigrostriatal denervation and L-Dopa Therapy on the GABAergic Neurons of the Striatum in MPTP-treated Monkeys and **Parkinson**'s Disease: An In Situ Hybridization Study of **GAD**-67 mRNA.
AUTHOR: Levy R; Herrero M T; Ruberg M; Villares J; Faucheux B; Guridi J; Guillen J; Luquin M R; Javoy-Agid F; Obeso J A; Agid Y; Hirsch E C(a)
AUTHOR ADDRESS: (a)INSERM U.289, Hopital Salpetriere, 47 boulevard l'Hopital, 75651 Paris Cedex 13**France
JOURNAL: European Journal of Neuroscience 7 (6):p1199-1209 1995
ISSN: 0953-816X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The effects of nigrostriatal denervation and L-dopa therapy on GABAergic neurons were analysed in patients with **Parkinson**'s disease and in monkeys rendered **parkinsonian** by MPTP intoxication. The expression of the messenger RNA coding for the 67 kDa isoform of glutamic acid decarboxylase (**GAD**-67 mRNA), studied by quantitative in situ hybridization, was used as an index of the GABAergic activity of the striatal neurons. A significant increase in **GAD**-67 mRNA expression, generalized to all GABAergic neurons, was observed in MPTP-treated monkeys compared to control monkeys in the putamen and caudate nucleus (+44 and +67% respectively), but not in the ventral

striatum. L-Dopa therapy significantly reduced **GAD**-67 mRNA expression in the putamen and caudate nucleus to levels similar to those found in control monkeys. However, the return to normal of **GAD**-67 mRNA expression was not homogeneous across all neurons since it was followed by an increase of labelling in one subpopulation of GABAergic neurons and a decrease in another. These data suggest that in MPTP-treated monkeys the degeneration of nigrostriatal dopaminergic neurons results in a generalized increase in GABAergic activity in all the GABAergic neurons of the striatum, which is partially reversed by L-dopa therapy. As the expression of **GAD**-67 mRNA is less intense in the ventral than in the dorsal striatum, this increase in striatal GABAergic activity may be related to the severity of nigrostriatal denervation. In **parkinsonian** patients who had been chronically treated with L-dopa, **GAD**-67 mRNA expression was significantly decreased in all GABAergic neurons, in the caudate nucleus (by 44%), putamen (by 43.5%) and ventral striatum (by 26%). The opposite variation of **GAD**-67 mRNA in patients with **Parkinson**'s disease, compared with MPTP-treated monkeys, might be explained by the combination of chronic nigrostriatal denervation and long-term L-dopa therapy.

1995

3/3,AB/61 (Item 23 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09008089 BIOSIS NO.: 199497016459
Decreased **GAD** mRNA expression in internal pallidum and substantia nigra pars reticulata neurons after subthalamotomy in MPTP treated monkeys.
AUTHOR: Guridi J(a); Herrero M-T(a); Ruberg M(a); Hirsch E C; Guillen J(a); Luquin M R(a); Javoy-Agid F; Agid Y; Obeso J A(a)
AUTHOR ADDRESS: (a)Neurol. Exper. Univ. Navarra, 31080 Pamplona**Spain
JOURNAL: Society for Neuroscience Abstracts 19 (1-3):p133 1993
CONFERENCE/MEETING: 23rd Annual Meeting of the Society for Neuroscience Washington, D.C., USA November 7-12, 1993
ISSN: 0190-5295
RECORD TYPE: Citation
LANGUAGE: English
1993

3/3,AB/62 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09008088 BIOSIS NO.: 199497016458
Changes in **GAD** mRNA expression in neurons of the internal pallidum in **parkinsonian** monkeys after L-dopa therapy.
AUTHOR: Herrero M-T(a); Ruberg M(a); Hirsch E C(a); Guridi J; Luquin M R; Guillen J; Javoy-Agid F(a); Agid Y(a); Obeso J A
AUTHOR ADDRESS: (a)INSERM U289, Hopital Salpetriere, 75651 Paris**France
JOURNAL: Society for Neuroscience Abstracts 19 (1-3):p132 1993
CONFERENCE/MEETING: 23rd Annual Meeting of the Society for Neuroscience Washington, D.C., USA November 7-12, 1993
ISSN: 0190-5295
RECORD TYPE: Citation
LANGUAGE: English
1993

3/3,AB/63 (Item 25 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07753570 BIOSIS NO.: 000092067291
L DOPA REPLACEMENT THERAPY ALTERS ENZYME ACTIVITIES IN STRIATUM AND NEUROPEPTIDE CONTENT IN STRIATAL OUTPUT REGIONS OF 6 HYDROXYDOPAMINE LESIONED RATS
AUTHOR: ENGBER T M; SUSEL Z; KUO S; GERFEN C R; CHASE T N
AUTHOR ADDRESS: NINDS, NIH, BUILD. 10, ROOM 5C103, 9000 ROCKVILLE PIKE, BETHESDA, MD. 20892, USA.
JOURNAL: BRAIN RES 552 (1). 1991. 113-118. 1991
FULL JOURNAL NAME: Brain Research
CODEN: BRREA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The effects of striatal dopamine denervation and levodopa replacement therapy on neuronal populations in the rat striatum were assessed by measurement of glutamic acid decarboxylase (**GAD**) and choline acetyltransferase (CAT) activities in the striatum, dynorphin and substance P concentrations in the substantia nigra, and enkephalin concentration in the globus pallidus. Rats with a unilateral 6-hydroxydopamine (6-OHDA) lesion of the nigrostriatal pathway were treated for 21 days with levodopa (100 mg/kg/day, i.p., with 25 mg/kg benserazide) on either an intermittent (b.i.d.) or continuous (osmotic pump infusion) regimen and sacrificed following a three day drug washout. In saline-treated control rats, striatal **GAD** activity and globus pallidus enkephalin content were elevated and nigral substance P content was reduced ipsilateral to the 6-OHDA lesion. Intermittent levodopa treatment further increased **GAD** activity, decreased CAT activity, restored substance P to control levels, markedly increased dynorphin content, and had no effect on enkephalin. In contrast, continuous levodopa elevated globus pallidus enkephalin beyond the levels occurring with denervation, but had no effect on any of the other neurochemical measures. These results indicate that striatal neuronal populations are differentially affected by chronic levodopa therapy and by the continuous or intermittent nature of the treatment regimen. With the exception of substance P, levodopa did not reverse the effects of the 6-OHDA lesion but, rather, either exacerbated the lesion-induced changes (e.g. **GAD** and enkephalin) or altered neurochemical markers which had been unaffected by the lesion (e.g. CAT and dynorphin). These findings suggest that chronic levodopa treatment may create a new functional state in the striatum which is different from both the normal state and the denervated state and may provide insight into the pathophysiology of the motor response complications which often accompany long-term levodopa therapy in **parkinsonian** patients.

1991

3/3,AB/64 (Item 26 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07340006 BIOSIS NO.: 000090119908
SEASONAL ABUNDANCE AND MARINE HABITATS OF PROCELLARIA FULMARINE AND **GADFLY** PETRELS OFF CENTRAL NEW SOUTH WALES AUSTRALIA
AUTHOR: WOOD K A
AUTHOR ADDRESS: 7 EASTERN AVE., MANGERTON 2500 NSW, AUST.
JOURNAL: NOTORNIS 37 (2). 1990. 81-105. 1990
FULL JOURNAL NAME: Notornis
CODEN: NTNSA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Between April 1985 and March 1987, standardised shipboard censuses were conducted during 23 monthly transects from shore to well

beyond the continental shelf. The average transect distance was 66 km and maximum depth 4200 [redacted]. Twelve (probably 13) species and 2311 birds were recorded. Regular petrels (listed in descending percentage abundance) had zonal and seasonal distributions as follows: Pterodroma macroptera (50%), pelagic, spring and summer; P. solandri (24%), pelagic, autumn, winter and spring: Daption capense (16%), neritic, winter and spring; Macronectes spp. [M. halli and M. giganteus] (5%), marginally neritic, winter and spring; small Pterodroma spp. ("Cookilaria") (4%), pelagic, summer and autumn; P. lessonii (1%), pelagic, autumn, winter and spring. Petrels rarely observed were Fulmarus glacialoides (1), Pterodroma neglecta (3), Procellaria **parkinsoni** (4) and Pseudobulweria rostrata (1). Temperature preferences, morphological characters, behaviour and breeding status are discussed. The 200+ "Cookilaria" observed during two cruises in April 1985 may have been associated with a slope-water intrusion by the East Australian Current.

1990

3/3,AB/65 (Item 27 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07250910 BIOSIS NO.: 000090030786
TRANSPLANTATION OF HUMAN FETAL DOPAMINE CELLS FOR **PARKINSON**'S DISEASE RESULTS AT 1 YEAR
AUTHOR: FREED C R; BREEZE R E; ROSENBERG N L; SCHNECK S A; WELLS T H; BARRETT J N; GRAFTON S T; HUANG S C; EIDELBERG D; ROTTENBERG D A
AUTHOR ADDRESS: DEP. MED., UNIV. COLORADO HEALTH SCI. CENTER, 4200 E. NINTH AVE., DENVER, COLO. 80262.
JOURNAL: ARCH NEUROL 47 (5). 1990. 505-512. 1990
FULL JOURNAL NAME: Archives of Neurology
CODEN: ARNEA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: In an effort to improve the clinical signs of **Parkinson**'s disease, we have implanted mesencephalic dopamine cells from a 7-week human embryo into the caudate and putamen of a 52-year-old man with **Parkinson**'s disease. Fetal tissue was obtained from elective abortion. The woman and the patient with **Parkinson**'s disease were unknown to each other. The woman gave specific consent and was not paid. The patient had a 20-year history of **parkinsonism** treated with multiple drug therapies including levodopa/carbidopa (Sinemet) every 2 1/2 hours. His symptoms were worse on the left side. For 5 months prior to transplantation, the patient underwent clinical evaluations by both a neurologist and a computer system installed in his home for daily measurement of walking and hand movements. Preoperative positron emission tomographic scanning with 6-L[18F]fluorodopa (fluorodopa) demonstrated severe dopamine depletion bilaterally. Fetal tissue was matched to the patient for ABO blood antigens, and maternal serum was screened for hepatitis and human immunodeficiency virus type 1 prior to surgery. Fetal tissue was implanted stereotactically throughout the caudate and putamen on the right side of the brain via 10 needle tracks. The patient was not immunosuppressed. Results 12 months after surgery showed 42% improvement in left-hand speed before the first morning dose of drug and 40% greater response to drug therapy. Right-hand speed increased 15% before drug therapy and 23% after drug therapy. Reaction time was unaffected. Walking speed increased 33% after drug administration, although walking speed before the first morniing dose of drugs declined 40%. Walking speed on an all-day basis improved 17%. "On" time increased from 69% to 86% of the day. For technical reasons, preoperative and postoperative fluorodopa positron emission tomographic scans were performed at different facilities, so that results could not be directly compared. A magnetic resonance scan 5 months after surgery showed that signs of the needle

tracks were still visible but that there was no enhanced signal after **gadolinium** injection, indicating that the blood-brain barrier was intact. These data indicate that transplants of human fetal dopamine cells may have therapeutic benefit in patients with **Parkinson**'s disease.

1990

3/3,AB/66 (Item 28 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

05658539 BIOSIS NO.: 000084006944
NEUROTRANSMITTERS AND DEGENERATIVE DISEASES IN THE CENTRAL NERVOUS SYSTEM
AUTHOR: NAKAMURA S
AUTHOR ADDRESS: DEP. NEUROL., FAC. MED., KYOTO UNIV., KYOTO.
JOURNAL: JPN J GERIATR 23 (1). 1986 (RECD. 1987). 11-16. 1986
FULL JOURNAL NAME: Japanese Journal of Geriatrics
CODEN: NIRZA
RECORD TYPE: Abstract
LANGUAGE: JAPANESE

ABSTRACT: Age-related changes in neurotransmitters were investigated, using cerebrospinal fluid or serum of control subjects. The concentration of homovanillic acid (HVA) and tetrahydrobiopterin in the cerebrospinal fluid showed an age-dependent decrease, indicating a decrease in dopaminergic activity in the aged. The concentration of 5-hydroxyindoleacetic acid (5-HIAA) was not changed significantly with the advance in the age. The activity of dopamine .beta.-hydroxylase (D.beta.H) in the cerebrospinal fluid (CSF) showed a wide variation among normal subjects and no significant age-related decrease was not observed. The D.beta.H activity in the serum was significantly lower in subjects older than 80 years. The activity of glutamic acid decarboxylase (**GAD**) in both CSF and serum also decreased according to the increase in the age, probably due to the decrease in the activity of GABAnergic neuron. The acetylcholine esterase (ACE) activity in the CSF increased significantly with the advance in age. The ACE activity in the CSF was decreased significantly in Alzheimer's disease with early onset. But 4 patients with senile dementia with later onset showed a higher ACE activity than normal subjects, while 7 patients showed lower ACE activity than control subjects. These results suggest that cholinergic system seems to be affected more severely in Alzheimer's disease than in senile dementia. Moreover, cholinergic system might be involved in the manifestation of dementia in **Parkinson**'s disease. The concentration of HVA in the CSF was decreased not only in patients with **Parkinson** 's disease but also in patients with pathological laughing and/or crying in motor neuron disease or spinocerebellar degeneration. Patients with Shy-Drager syndrome showed a decreased serum D.beta.H activity. The concentration of 5-HIAA was decreased in the CSF of **parkinsonian** patients with hallucination. Serum **GAD** activity was decreased in advanced cases of **Parkinson**'s disease as well as in Huntington's disease. The age-related changes in neurotransmitters seem to provide a ground for degenerative diseases in central nervous system. However, a causative agent such as N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine may induce the degenerative disease in the central nervous system, while reactive changes may take place to counteract the degeneration. The deficit of the sole neurotransmitters is responsible for the early stage of the degenerative disease. The disturbance in other neurotransmitters is introduced according to the progress of the disease and presents additional symptoms, such as hallucination, autonomic symptoms or dementia in **Parkinson**'s disease.

1986

3/3,AB/67 (Item [redacted] from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

05658406 BIOSIS NO.: 000084006811
DOPAMINERGIC AXONS DIRECTLY MAKE SYNAPSES WITH GABAERGIC NEURONS IN THE RAT NEOSTRIATUM
AUTHOR: KUBOTA Y; INAGAKI S; KITO S; WU J-Y
AUTHOR ADDRESS: THIRD DEP. INTERNAL MED., HIROSHIMA UNIV. SCH. MED., 1-2-3 KASUMI, MINAMI-KU, HIROSHIMA 734, JPN.
JOURNAL: BRAIN RES 406 (1-2). 1987. 147-156. 1987
FULL JOURNAL NAME: Brain Research
CODEN: BRREA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We examined with an electron microscopic 'mirror technique' whether glutamic acid decarboxylase-immunoreactive (**GAD**-IR) neurons are in direct synaptic contact with tyrosine hydroxylase-immunoreactive (TH-IR) axons in the rat neostriatum. Three types of **GAD**-IR neurons were identified in the nucleus caudatus putamen based upon their size and ultrastructural characteristics. These were medium spiny, medium aspiny and large cells. All types of **GAD**-IR neurons made synaptic contact with TH-IR axonal boutons at least on perikarya and proximal dendrites. This provides ultrastructural evidence for catecholaminergic, presumably, nigrostriatal dopaminergic inputs to both long- and short-axon neurons most probably containing GABA.

1987

3/3,AB/68 (Item 30 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

03965451 BIOSIS NO.: 000076051017
STRIATAL GAMMA AMINO BUTYRIC-ACID-ERGIC NEURONAL ACTIVITY IS NOT REDUCED IN **PARKINSON** DISEASE
AUTHOR: PERRY T L; JAVOY-AGID F; AGID Y; FIBIGER H C
AUTHOR ADDRESS: DEP. PHARMACOL., UNIV. BRITISH COLUMBIA, VANCOUVER V6T 1W5, CANADA.
JOURNAL: J NEUROCHEM 40 (4). 1983. 1120-1123. 1983
FULL JOURNAL NAME: Journal of Neurochemistry
CODEN: JONRA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The content of GABA and the activities of glutamic acid decarboxylase (**GAD**) and tyrosine hydroxylase (TH) were measured in whole putamen obtained at autopsy from 13 patients dying with idiopathic **Parkinson**'s disease and 13 appropriate control subjects. Mean GABA content was significantly elevated (by 28%) in the putamen of the **Parkinson**'s disease patients. TH activity was markedly reduced, while there was no significant reduction of **GAD** activity in the putamen of these patients. GABA content was also measured in both sides of the striatum in rats which had received unilateral injections of 6-hydroxydopamine (6-OHDA) in the vicinity of the axons of the nigrostriatal projection. Mean GABA content was found significantly elevated (by 33%) in the ipsilateral striatum. Loss of dopaminergic nigrostriatal neurons, in both human **Parkinson**'s disease and in the rat 6-OHDA model, is accompanied by increased striatal GABA content. The assumption that GABAergic neurotransmission is reduced in the striatum in **Parkinson**'s disease may not be correct.

1983

3/3,AB/69 (Item 31 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

03559855 BIOSIS NO.: 000073062936
MICRO TOPOGRAPHY OF TYROSINE HYDROXYLASE GLUTAMIC-ACID DECARBOXYLASE AND CHOLINE ACETYL TRANSFERASE IN THE SUBSTANTIA NIGRA AND VENTRAL TEGMENTAL AREA OF CONTROL AND **PARKINSONIAN** BRAINS
AUTHOR: JAVOY-AGID F; PLOSKA A; AGID Y
AUTHOR ADDRESS: LABORATOIRE DE MEDECINE EXPERIMENTALE, UER PITIE-SALPETRIERE, 91, BOULEVARD DE L'HOPITAL, 75634, PARIS, CEDEX 13, FRANCE.
JOURNAL: J NEUROCHEM 37 (5). 1981. 1218-1227. 1981
FULL JOURNAL NAME: Journal of Neurochemistry
CODEN: JONRA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Tyrosine hydroxylase (TH), glutamic acid decarboxylase (**GAD**) and choline acetyltransferase (CAT) were used as markers for catecholamine, GABA and acetylcholine containing neurons in human mesencephalon. Their rostrocaudal, mediolateral and dorsoventral distribution was investigated within the substantia nigra pars compacta (SNC) and pars reticulata (SNR) and in the ventral tegmental area (VTA). TH activity was highest in the caudal, medial and ventral SNC and in the middle of VTA medioventrally. The enzyme activity in SNR was low and uniformly distributed. In SNC and SNR, **GAD** activity was high and greater laterally and in the middle of the rostrocaudal extent. No particular pattern of distribution was observed in VTA, an area with low **GAD** content. In the substantia nigra, CAT activity was low. A characteristic medioventral distribution with a peak of high enzyme activity in the middle of the rostrocaudal extent was observed. In VTA, enzyme levels were high and also concentrated medioventrally and in the middle of the area. In **parkinsonian** brains, the distribution of TH was uniformly affected throughout the rostrocaudal extent. In VTA the enzyme activity was not as reduced as in SNC and SNR; the CAT pattern was only disrupted in a very localized part of SNC but not in SNR and VTA. In all 3 areas, **GAD** activity was reduced to a uniformly low distribution.

1981

3/3,AB/70 (Item 32 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

02958299 BIOSIS NO.: 000069066417
REGIONAL DISTRIBUTION OF NEURO TRANSMITTER SYNTHESIZING ENZYMES IN THE BASAL GANGLIA OF HUMAN BRAIN
AUTHOR: GASPAR P; JAVOY-AGID F; PLOSKA A; AGID Y
AUTHOR ADDRESS: LAB. MED. EXP., CENT. HOSP. UNIV. PITIE-SALPETRIERE, 91 BLVD. L'HOPITAL, 75634 PARIS-CEDEX 13, FR.
JOURNAL: J NEUROCHEM 34 (2). 1980. 278-283. 1980
FULL JOURNAL NAME: Journal of Neurochemistry
CODEN: JONRA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Tyrosine hydroxylase (TH, EC 1.14.16.2), glutamate decarboxylase (**GAD**, EC 4.1.1.15), and choline acetyltransferase (ChAT, EC 2.3.1.6), activities were used as markers of catecholaminergic, GABAergic

and cholinergic neurons in human brain. The disparity in the absolute values obtained in control caudate nucleus led to the study of the pattern of distribution of these enzymes in given brain regions, with the idea that the pattern might be altered specifically in pathological conditions. The 3-dimensional distribution of TH, **GAD**, and ChAT activities was investigated within the caudate nucleus, the putamen and the pallidum. In control patients, opposite rostro-caudal and medio-lateral gradients appeared for **GAD** and CAT; ChAT activity was higher at the caudal level and **GAD** activity was higher at the rostral level of caudate nucleus and putamen. In the medio-lateral extent of putamen and pallidum, ChAT activity was highest in the lateral part of the putamen; **GAD** was highest in the medial segment of the pallidum. Only **GAD** presented a particular dorso-ventral pattern, the enzyme activity being highest in the ventral part of the caudate nucleus and the putamen. No reproducible distribution was observed for TH. In **Parkinsonian** patients, a decrease of TH and **GAD** activities with abolition of gradients was observed, whereas the ChAT activity and pattern were not modified.

1980

3/3,AB/71 (Item 33 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

02631055 BIOSIS NO.: 000067019116
INCREASED GAMMA AMINO BUTYRIC-ACID CONTENT IN CAUDATE NUCLEUS OF RATS AFTER CHRONIC MANGANESE CHLORIDE ADMINISTRATION
AUTHOR: BONILLA E
AUTHOR ADDRESS: NEUROCHEM. SECT., INST. INVEST. CLIN., FAC. MED., UNIV. ZULIA, APDO. 1151, MARACAIBO, VENEZ.
JOURNAL: J NEUROCHEM 31 (2). 1978 551-552. 1978
FULL JOURNAL NAME: Journal of Neurochemistry
CODEN: JONRA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Studies on the distribution of .gamma. aminobutyric acid (GABA) in the mammalian brain have shown that the substantia nigra and the caudate nucleus are among the areas containing the highest concentrations of this putative inhibitory neurotransmitter. This and other evidence suggest the existence of an inhibitory striato-nigral GABA-ergic neuronal system formed by neurons whose cell bodies lie in the caudate nucleus and whose synaptic terminals are in contact with nigro-striatal dopaminergic neurons. In view of the described relationship, any alteration in striatal dopamine turnover could produce changes in brain GABA metabolism and vice versa. A dopamine deficiency and a decrease in glutamic acid decarboxylase (**GAD**) activity have been demonstrated in the substantia nigra, caudate nucleus and putamen of **Parkinsonian** patients. On the other hand, it is known that chronic Mn poisoning is characterized by psychiatric and neurological symptoms, often encountered in **Parkinson**'s disease. These observations and the finding of a brain dopamine deficiency in chronic Mn poisoning led to testing of the effect of chronic Mn intake on the metabolism of GABA in rat caudate nucleus. As a result of the lowered synthesis of dopamine in chronic Mn poisoning, the inhibition of GABA outflow at nigral dopaminergic neurons might occur by a feedback mechanism which would tend to favor the striatal release of dopamine.

1978

3/3,AB/72 (Item 34 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

02483666 BIOSIS NO.: 000066066219
GABA GAMMA AMINO BUTYRIC-ACID AND EXTRAPYRAMIDAL DISEASES
AUTHOR: CARRIERI P
AUTHOR ADDRESS: CLIN. NEUROL., II FAC. MED. CHIR., UNIV. NAPOLI, NAPOLI, ITALY.
JOURNAL: ACTA NEUROL (NAPLES) 32 (5). 1977 (RECD 1978) 697-704. 1977
FULL JOURNAL NAME: Acta Neurologica (Naples)
CODEN: ACNLA
RECORD TYPE: Abstract
LANGUAGE: ITALIAN

ABSTRACT: Metabolism of GABA, the major inhibitory neurotransmitter in the nervous system, and its enzyme glutamine decarboxylase (**GAD**) action; GABA and **GAD** concentrations in the basal ganglia and correlations between GABA and other neurotransmitters were evaluated. Starting from GABA and **GAD** decreasing in the basal ganglia, some pathogenetic remarks on **Parkinson**'s disease and Huntington's chorea are emphasized.

1977

3/3,AB/73 (Item 35 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

01959919 BIOSIS NO.: 000062050029
ENZYMES ASSOCIATED WITH THE METABOLISM OF CATECHOLAMINES ACETYL CHOLINE AND GAMMA AMINO BUTYRIC-ACID IN HUMAN CONTROLS AND PATIENTS WITH **PARKINSONS** DISEASE AND HUNTINGTONS CHOREA
AUTHOR: MCGEER P L; MCGEER E G
JOURNAL: J NEUROCHEM 26 (1). 1976 65-76. 1976
FULL JOURNAL NAME: Journal of Neurochemistry
CODEN: JONRA
RECORD TYPE: Abstract

ABSTRACT: Tyrosine hydroxylase (TH), dopa decarboxylase (DDC), glutamic acid decarboxylase (**GAD**), choline acetyltransferase (CAT) and acetylcholinesterase (AChE) were measured in 18-55 areas of brain from humans post mortem. Individuals meeting sudden and unexpected death (22), patients dying in hospital with non-neurological illness (6), **Parkinson**'s disease (12), Huntington's chorea (8), terminal coma (6) or head injury (2) were included in the series. The absolute values obtained compared favorably with some previous human studies where high values for these enzymes were obtained, and with monkey and baboon data. The regional distributions of the enzymes were also comparable to those previously reported in human and animal studies. The mode of death was not a factor in enzyme levels in non-neurological and non-coma cases. Post mortem delay did not seem to be a major factor either even though a substantial decline in **GAD**, TH and DDC could be demonstrated in rats left several hours between sacrifice and removal of the brain for assay. Age had a highly significant effect in certain areas of brain. The decline typically followed a curvilinear pattern (activity = A/age + B with the sharpest drops being in the younger age groups). DDC seemed to be the enzyme most severely affected by age but all the enzymes showed declines in certain brain areas, while in other areas there was no significant decline. All the enzymes were very depressed by coma from illness except AChE. TH and DDC in the brain stem were not affected in the head injury cases. The **Parkinsonian** cases showd a sharply decreased TH activity in the substantia nigra, caudate and putamen. There were decreases in **GAD** in the globus pallidus (GP) and substantia nigra with marginal decreases in the neostriatum. CAT levels in the extrapyramidal nuclei were normal. In Huntington's chorea there was a

substantial decrease in **GAD** in all the extrapyramidal structures. There was a patchy loss of CAT in the neostriatum and locus coeruleus.

1976

3/3,AB/74 (Item 36 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

01937643 BIOSIS NO.: 000062027741
NORMAL GLUTAMIC DECARBOXYLASE EC-4.1.1.15 ACTIVITY IN RAT STRIATUM AND RETINA FOLLOWING ADMINISTRATION OF L DOPA
AUTHOR: TUNNICLIFF G; BUTTERWORTH R F; TSUKADA Y; BARBEAU A
JOURNAL: CAN J PHYSIOL PHARMACOL 54 (2). 1976 79-82. 1976
FULL JOURNAL NAME: Canadian Journal of Physiology and Pharmacology
CODEN: CJPPA
RECORD TYPE: Abstract

ABSTRACT: Recent reports of the in vivo action of L-dopa on glutamic acid decarboxylase (**GAD**) [EC 4.1.1.15] activity are contradictory. Both acute (100 mg/kg and 1 g/kg) and chronic (1 g/kg) i.p. administration of L-dopa to rats failed to produce any alteration in the activity of striatal or retinal **GAD** activity. These results are discussed in the light of a report relating L-dopa therapy to modification of **GAD** activity in **Parkinson**'s disease.

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           28424  GAD?
      S2      94  PARKINSON? AND GAD?
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...examined 50 records  (50)
...completed examining records
      S3      74  RD (unique items)
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 3/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11791307   21418688   PMID: 11529246
   Subthalamic  GAD gene transfer in Parkinson disease patients
who are candidates for deep brain stimulation.
  During MJ; Kaplitt MG; Stern MB; Eidelberg D
  Human gene therapy (United States)  Aug 10 2001,  12  (12)  p1589-91,
ISSN 1043-0342  Journal Code: A12
  Languages: ENGLISH
  Document type: Clinical Trial; Journal Article; Randomized Controlled
Trial
  Record type: Completed
  This gene transfer experiment is the first Parkinson's Disease (PD)
protocol to be submitted to the Recombinant DNA Advisory Committee. The
principal investigators have uniquely focused their careers on both
pre-clinical work on gene transfer in the brain and clinical expertise in
management and surgical treatment of patients with PD. They have
extensively used rodent models of PD for proof-of-principle experiments on
the utility of different vector systems. PD is an excellent target for gene
therapy, because it is a complex acquired disease of unknown etiology
(apart from some rare familial cases) yet it is characterized by a specific
neuroanatomical pathology, the degeneration of dopamine neurons of the
substantia nigra (SN) with loss of dopamine input to the striatum. This
pathology results in focal changes in the function of several deep brain
nuclei, which have been well-characterized in humans and animal models and
which account for many of the motor symptoms of PD. Our original
approaches, largely to validate in vivo gene transfer in the brain, were
designed to facilitate dopamine transmission in the striatum using an AAV
vector expressing dopamine-synthetic enzymes. Although these confirmed the
safety and potential efficacy of AAV, complex patient responses to dopamine
augmenting medication as well as poor results and complications of human
transplant studies suggested that this would be a difficult and potentially
dangerous clinical strategy using current approaches. Subsequently, we and
others investigated the use of growth factors, including GDNF. These showed
some encouraging effects on dopamine neuron survival and regeneration in
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administration of d[redacted]minergic drugs given days apa[redacted](priming). In situ hybridization was [redacted] to evaluate changes on striat[redacted]gene expression of rats primed three days previously with either L-dopa, SKF38393 or quinpirole. Double labeling was used to identify the neuronal population in which such alterations occurred. **GAD67** and enkephalin mRNA were increased by the lesion whereas dynorphin mRNA was decreased as compared to the intact striatum. Priming with L-dopa and SKF38393 significantly increased **GAD67** mRNA in the lesioned striatum and reversed dynorphin mRNA reduction, as compared to drug-naive rats, whereas quinpirole failed to produce any effect. Enkephalin mRNA was not affected by priming. Results suggest that 6-OHDA lesion-induced adaptive changes on striatal gene expression are modified by priming. Priming brings striatal output neurons to a higher level of activity, which may explain the sensitized behavioral response observed following a dopaminergic agonist challenge. These changes are in relation to the different types of dopamine agonists utilized and suggest that modifications in gene expression induced by priming might be predictive of the dyskinetic potential of a drug.

3/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11195763 21036791 PMID: 11180502
Traditional and new antipsychotic drugs differentially alter neurotransmission markers in basal ganglia-thalamocortical neural pathways.
Sakai K; Gao XM; Hashimoto T; Tamminga CA
Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore 21228, USA.
Synapse (United States) Feb 2001, 39 (2) p152-60, ISSN 0887-4476 Journal Code: VFL
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The effects of three chronically administered antipsychotic drugs on selected neurochemical markers of dopaminergic and GABAergic transmission were compared within the cerebral regions making up the basal ganglia-thalamocortical parallel processing neuronal pathways. All three drugs reduce psychosis in humans, whereas only haloperidol, but not olanzapine or sertindole, induce purposeless oral chewing movements (CMs) in rats or cause high rates of **parkinsonism** or tardive dyskinesia in humans. Male Sprague Dawley rats were treated with haloperidol, sertindole, or olanzapine delivered in drinking water for 6 months at doses which produce drug plasma levels in rat in the human therapeutic range. Results show the expected dopamine D2 receptor upregulation in striatum predominantly with haloperidol, although mild D2 upregulation was apparent in striatum after olanzapine. **GAD67** mRNA was increased in striatum and decreased in globus pallidus by haloperidol and sertindole, but not by olanzapine. In the substantia nigra pars reticulata (SNR), both olanzapine and sertindole failed to induce GABA(A) receptor upregulation or D1 receptor downregulation, but haloperidol did both, confirming a previous report. In thalamus, all three drugs increased **GAD** expression in the reticular nucleus, whereas only haloperidol decreased GABA(A) binding in the mediodorsal nucleus, actions consistent with a reduction in nigrothalamic, GABA-mediated neural transmission. These results are consistent with the idea that the two new antipsychotics tested have mild and regionally restricted actions within the basal ganglia nuclei and a common action on increasing **GAD** expression in the reticular nucleus of the thalamus (RtN). Haloperidol, in contrast, has a broad and potent action in basal ganglia, causing changes in SNR and in the mediodorsal nucleus, while also altering **GAD** mRNA in RtN, potentially reflective of its dyskinetic and antipsychotic actions.

3/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09740535 98197141 PMID: 9527896
Toxicity of dieldri[redacted]or dopaminergic neurons in mes[redacted]ephalic cultures.
Sanchez-Ramos J; Facca A; Basit A; Song S
Department of Neurology, University of South Florida, James A. Haley VA Medical Center, Research 151, 13000 Bruce B Downs Boulevard, Tampa, Florida 33612, USA.
Experimental neurology (UNITED STATES) Apr 1998, 150 (2) p263-71, ISSN 0014-4886 Journal Code: EQF
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Dieldrin can be retained for decades in lipid-rich tissue and has been measured in some postmortem PD brains. Dieldrin has been reported to deplete brain monoamines in several species and has been shown to inhibit mitochondrial respiration. To further investigate the possibility that it may be involved in the pathogenesis of **parkinsonism**, its toxicity for dopaminergic (DA) neurons was assessed in a mesencephalic cell culture model. Primary neuronal cultures of mesencephalic neurons were prepared from fetal rats or fetal mice, grown for 1 week and incubated with Dieldrin (0.01-100 microM) for 24 or 48 h. Toxicity for DA neurons was determined by measuring density of surviving tyrosine hydroxylase immunoreactive (TH-ir) cells. Toxicity for gamma-aminobutyric acid (GABA)-ergic neurons was determined by measuring survival of glutamate decarboxylase (**GAD**)-ir neurons. General, nonselective cytotoxicity was determined by counting cells visualized by phase contrast microscopy or by DAPI-stained cells with fluorescence microscopy. Dieldrin exposure for 24 h resulted in a dose-dependent decrease in survival of TH-IR cells (DA neurons) with a 50% decrease (EC50) produced by 12 microM in rat mesencephalic cultures. Dieldrin also produced a dose- and time-dependent decrease in mouse DA-ergic and GABA-ergic neurons in mouse mesencephalic cultures. GABA-ergic neurons were less sensitive to the toxin compared to DA-ergic neurons. Cellular uptake of 3H-DA was also affected by lower concentrations of Dieldrin (EC50 = 7.98 microM) than uptake of 3H-GABA (EC50 = 43 microM). Thus, Dieldrin appears to be a relatively selective DA-ergic neurotoxin in mesencephalic cultures. Dieldrin, which may be ubiquitous in the environment, is proposed as an agent which can initiate and promote dopaminergic neurodegeneration in susceptible individuals. Copyright 1998 Academic Press.

3/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09594274 97410058 PMID: 9266773
Glutamate decarboxylase (**GAD67** and **GAD65**) gene expression is increased in a subpopulation of neurons in the putamen of **Parkinsonian** monkeys.
Soghomonian JJ; Laprade N
Centre de Recherche en Neurobiologie et Departement d'Anatomie, Faculte de Medecine, Universite Laval, Quebec, Canada. Jean-Jacques.Soghomonian@anm.ulaval.ca
Synapse (UNITED STATES) Oct 1997, 27 (2) p122-32, ISSN 0887-4476 Journal Code: VFL
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The cellular distribution of the mRNAs encoding for the two isoforms of glutamate decarboxylase, **GAD67** and **GAD65**, was analyzed by in situ hybridization histochemistry in the caudate nucleus and putamen of control and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated **parkinsonian** squirrel monkeys. On brain sections processed with a radioactive and a digoxigenin-labeled cRNA probe, the **GAD67** and **GAD65** mRNAs were colocalized in virtually all labeled neurons of the caudate nucleus and putamen, in both control and MPTP-treated monkeys. Furthermore, neurons labeled with the **GAD** cRNAs constituted at least

90% of all striatal neurons, as estimated on adjacent Nissl-stained sections. In the two groups of monkeys, double-labeling experiments using a combination of radioactive **GAD67** or **GAD65** and digoxigenin-labeled preproenkephalin (PPE) cRNA probes showed that roughly half of all neurons labeled with the **GAD** cRNAs were also labeled with the PPE cRNA probe. When compared to controls, **GAD67** and **GAD65** mRNA levels were higher in the putamen, and to a lesser extent in the caudate nucleus, of MPTP-treated monkeys. Further analysis of labeling at the cellular level in a dorsolateral sector of the putamen revealed that **GAD67** and **GAD65** mRNA levels in MPTP-treated monkeys were increased in PPE-labeled (presumed striato-pallidal) neurons but not in PPE-unlabeled (presumed striato-nigral) neurons. Our results demonstrate that most neurons in the caudate nucleus and putamen of squirrel monkeys contain the mRNAs encoding for the two **GAD** isoforms. In addition, the selective increase in **GAD** mRNA levels in PPE-labeled neurons provides further evidence that striato-pallidal GABAergic neurons are hyperactive in MPTP-treated **parkinsonian** monkeys.

3/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09216970 96291044 PMID: 8710082
Consequence of nigrostriatal denervation and L-dopa therapy on the expression of glutamic acid decarboxylase messenger RNA in the pallidum.
Herrero MT; Levy R; Ruberg M; Luquin MR; Villares J; Guillen J; Faucheux B; Javoy-Agid F; Guridi J; Agid Y; Obeso JA; Hirsch EC
Department of Experimental Neurology, University of Navarra, Pamplona, Spain.
Neurology (UNITED STATES) Jul 1996, 47 (1) p219-24, ISSN 0028-3878 Journal Code: NZ0
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
To examine the consequences of nigrostriatal denervation and L-dopa treatment on the basal ganglia output system, we analyzed, by quantitative in situ hybridization, the messenger RNA coding for glutamic acid decarboxylase (Mr 67,000) (**GAD67** mRNA) in pallidal cells from patients with **Parkinson**'s disease (PD), monkeys rendered **parkinsonian** by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) receiving or not receiving L-dopa, and their respective control subjects. In MPTP-treated monkeys, the expression of **GAD67** mRNA was increased in cells from the internal pallidum, and this effect was abolished by L-dopa treatment. There were no differences in the levels of **GAD67** mRNA between patients with PD, who were all treated with L-dopa, and control subjects. These results indicate that the level of **GAD67** mRNA is increased in the cells of the internal pallidum after nigrostriatal dopaminergic denervation and that this increase can be reversed by L-dopa therapy.

3/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09179629 97185134 PMID: 9032875
Lesion size following Gamma Knife treatment for functional disorders.
Friehs GM; Noren G; Ohye C; Duma CM; Marks R; Plombon J; Young RF
Department of Neurosurgery, Brown University, Providence, R.I., USA.
Stereotactic and functional neurosurgery (SWITZERLAND) 1996, 66 Suppl 1 p320-8, ISSN 1011-6125 Journal Code: SFN
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
In this study we investigated the reproducibility and consistency of the size of radiosurgical lesions produced for functional disorders. The T1

Consequences of nigrostriatal denervation on the gamma-aminobutyric acidic neurons of substantia nigra pars reticulata and superior colliculus in **parkinsonian** syndromes.

Vila M; Herrero MT; Levy R; Faucheux B; Ruberg M; Guillen J; Luquin MR; Guridi J; Javoy-Agid F; Agid Y; Obeso JA; Hirsch EC

INSERM U289, Hopital de la Salpetriere, Paris, France.

Neurology (UNITED STATES) Mar 1996, 46 (3) p802-9, ISSN 0028-3878 Journal Code: NZ0

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

To examine the effects of nigrostriatal denervation on the substantia nigra pars reticulata (SNpr), one of the main outputs of the basal ganglia, we used quantitative in situ hybridization to analyze the messenger RNA coding for Mr 67,000 glutamic acid decarboxylase (**GAD67** mRNA) in the SNpr neurons from patients with **Parkinson**'s disease (PD), monkeys rendered **parkinsonian** by 1-methyl-4- phenyl-1,2,3,6-tetrahydropyridin e (MPTP), and their respective controls. In MPTP-intoxicated monkeys, the expression of **GAD67** mRNA was increased in the SNpr neurons, and the increase was reversed by L-dopa treatment. There were no differences in the level of **GAD67** mRNA between PD patients who had been treated with L-dopa and control subjects. Combined with the previously reported increased expression of **GAD67** mRNA in the internal segment of the pallidum of MPTP-intoxicated monkeys, these data suggest that the gamma-aminobutyric acid (GABAergic) activity of the output system of the basal ganglia is globally increased by nigrostriatal denervation. We also analyzed the level of **GAD67** mRNA expression in the superior colliculus, a structure that receives the inhibitory influence of the GABAergic neurons of the SNpr and that is involved in eye movement control. **GAD67** mRNA expression was reduced in both MPTP-intoxicated monkeys, whether or not they received L-dopa therapy, and PD patients, compared to their respective controls. This decrease may result from the hyperactivity of the inhibitory nigrotectal pathway, but also from other influences since it was not corrected by L-dopa therapy. These changes may account for the slight ocular motor and visuospatial cognitive impairment occurring in PD, even after L-dopa therapy.

3/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08903327 96073228 PMID: 7582093

Effects of nigrostriatal denervation and L-dopa therapy on the GABAergic neurons in the striatum in MPTP-treated monkeys and **Parkinson**'s disease: an in situ hybridization study of **GAD67** mRNA.

Levy R; Herrero MT; Ruberg M; Villares J; Faucheux B; Guridi J; Guillen J ; Luquin MR; Javoy-Agid F; Obeso JA; et al

INSERM U.289, Hopital de la Salpetriere, Paris, France.

European journal of neuroscience (ENGLAND) Jun 1 1995, 7 (6) p1199-209, ISSN 0953-816X Journal Code: BYG

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The effects of nigrostriatal denervation and L-dopa therapy on GABAergic neurons were analysed in patients with **Parkinson**'s disease and in monkeys rendered **parkinsonian** by MPTP intoxication. The expression of the messenger RNA coding for the 67 kDa isoform of glutamic acid decarboxylase (**GAD67** mRNA), studied by quantitative in situ hybridization, was used as an index of the GABAergic activity of the striatal neurons. A significant increase in **GAD67** mRNA expression, generalized to all GABAergic neurons, was observed in MPTP-treated monkeys compared to control monkeys in the putamen and caudate nucleus (+44 and +67% respectively), but not in the ventral striatum. L-Dopa therapy significantly reduced **GAD67** mRNA expression in the putamen and caudate nucleus to levels similar to those found in control monkeys.

However, the return to normal of **GAD67** mRNA expression was not homogeneous across neurons since it was followed by an increase of labelling in one subpopulation of GABAergic neurons and a decrease in another. These data suggest that in MPTP-treated monkeys the degeneration of nigrostriatal dopaminergic neurons results in a generalized increase in GABAergic activity in all the GABAergic neurons of the striatum, which is partially reversed by L-dopa therapy. As the expression of **GAD67** mRNA is less intense in the ventral than in the dorsal striatum, this increase in striatal GABAergic activity may be related to the severity of nigrostriatal denervation. In **parkinsonian** patients who had been chronically treated with L-dopa, **GAD67** mRNA expression was significantly decreased in all GABAergic neurons, in the caudate nucleus (by 44%), putamen (by 43.5%) and ventral striatum (by 26%). The opposite variation of **GAD67** mRNA in patients with **Parkinson**'s disease, compared with MPTP-treated monkeys, might be explained by the combination of chronic nigrostriatal denervation and long-term L-dopa therapy.

3/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08863130 95017005 PMID: 7931578

Increased glutamate decarboxylase mRNA levels in the striatum and pallidum of MPTP-treated primates.

Soghomonian JJ; Pedneault S; Audet G; Parent A

Centre de Recherche en Neurobiologie, Faculte de medecine, Universite Laval, Quebec, Canada.

Journal of neuroscience (UNITED STATES) Oct 1994, 14 (10) p6256-65, ISSN 0270-6474 Journal Code: JDF

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The mRNA levels encoding for the enzyme glutamate decarboxylase (**GAD67**) were measured by computerized image analysis after in situ hybridization histochemistry and radioautography in the striatum and pallidum of normal squirrel monkeys (Saimiri sciureus), or after treatment with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). All MPTP-injected monkeys exhibited profound motor deficits including akinesia. The dopaminergic innervation, as visualized and quantified on x-ray films after 3H-mazindol binding on tissue sections, was uniformly lost throughout the striatum of MPTP-treated monkeys. Brain sections processed with a probe synthesized from a feline or human **GAD67** cDNA exhibited intense radioautographic labeling throughout the striatum. When measured on x-ray films, the intensity of **GAD67** mRNA labeling was increased in the striatum of MPTP-treated versus control monkeys. Increased labeling reached statistical significance in the dorsolateral sector of the rostral putamen and throughout the putamen and the caudate at the caudal, postcommissural, level. Analysis of emulsion radioautographs demonstrated that the increase in **GAD67** mRNA labeling in MPTP-treated monkeys occurred in individual neurons of the striatum. In the external and internal segments of the pallidum, numerous neurons labeled with the **GAD67** cRNA probe were visualized on emulsion radioautographs. The intensity of **GAD67** mRNA labeling in single neurons of both pallidal segments was increased in MPTP-treated versus control monkeys. Construction of the histograms of frequency distribution of labeling indicated that this increase occurred in a majority of labeled neurons. The present study demonstrates that **GAD67** mRNA levels are significantly altered in the striatum and pallidum of **parkinsonian** monkeys. The preferential increase of **GAD67** mRNA labeling in the dorsolateral putamen, which receives afferents from the sensorimotor cortex, provides further evidence of the involvement of GABAergic transmission in the expression of the motor deficits elicited after MPTP. In addition, increased **GAD67** mRNA levels in the internal segment of the pallidum support the hypothesis of an increased activity of GABAergic neurons in the output structures of the basal ganglia in **parkinsonism**.

10971253 21066565 PMID: 11146067
Alterations in expression of messenger RNAs encoding two isoforms of glutamic acid decarboxylase in the globus pallidus and entopeduncular nucleus in animals symptomatic for and recovered from experimental **Parkinsonism**.
Schroeder JA; Schneider JS
Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA, USA.
Brain research (Netherlands) Jan 5 2001, 888 (1) p180-183, ISSN 0006-8993 Journal Code: B5L
Contract/Grant No.: NS23980, NS, NINDS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Glutamic acid decarboxylase (**GAD65**, **GAD67**) mRNA expression was measured in the globus pallidus (GP) and entopeduncular nucleus (ENTO) of normal, and MPTP-lesioned cats symptomatic for and recovered from MPTP-induced **Parkinsonism**. In the ENTO of symptomatic cats, **GAD65** and **GAD67** mRNA expression were both significantly increased, while only **GAD67** gene expression was increased in the GP. Levels of gene expression for both isoforms were normal in the GP and ENTO of spontaneously recovered animals. Increased expression of **GAD65**/67 mRNA in the ENTO corresponded with expression of **Parkinsonian** signs, suggesting a contribution of both isoforms to ENTO functioning and perhaps a greater contribution of **GAD67** expression to GP functioning.

3/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10690674 20362972 PMID: 10907726
Chronic supranigral infusion of BDNF in normal and MPTP-treated common marmosets.
Pearce RK; Costa S; Jenner P; Marsden CD
Neurodegenerative Diseases Research Centre, Biomedical Sciences Division, King's College London, and The National Hospital for Neurology, United Kingdom.
Journal of neural transmission (AUSTRIA) 1999, 106 (7-8) p663-83, Journal Code: CIJ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
BDNF or vehicle were administered by unilateral supranigral infusion in normal and chronically lesioned MPTP-treated common marmosets (Callithrix jacchus) for four weeks and locomotor activity, disability and response to apomorphine were assessed with nigral TH, GFAP and **GAD** immunoreactivity and striatal [3H]mazindol autoradiography. Selective contraversive orientation and ipsilateral neglect evolved in MPTP-treated marmosets receiving BDNF with no significant difference in disability or locomotor activity when compared to the vehicle-infused group. Apomorphine produced an ipsiversive rotational bias in BDNF-treated animals. In normal animals infused with BDNF contralateral neglect, ipsiversive turning, postural instability and ataxia rapidly evolved. In MPTP-treated marmosets BDNF caused increased ipsilateral striatal [3H]mazindol binding with increased somatic size and staining intensity in **GAD**-immunoreactive cells and a 10-20% loss of nigral TH-immunoreactive cells with increased GFAP staining. In normal common marmosets, both vehicle and BDNF infusion decreased nigral TH-immunoreactivity. Chronic supranigral infusion of BDNF alters motor behaviour and spatial attention in MPTP-treated marmosets which may reflect altered function in residual nigral dopaminergic neurons and brainstem GABAergic neurons and in normal animals produces behavioural and histological signs of nigrostriatal hypofunction.

3/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10673683 20286381 PMID: 10825495
Effects of a unilateral stereotaxic injection of Tinuvin 123 into the substantia nigra on the nigrostriatal dopaminergic pathway in the rat.
Jackson-Lewis V; Liberatore G
Columbia University, Department of Neurology, Neuroscience Research, New York, NY 10032, USA. vrj1@columbia.edu
Brain research (NETHERLANDS) Jun 2 2000, 866 (1-2) p197-210, ISSN 0006-8993 Journal Code: B5L
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Tinuvin 123, a compound used in the manufacture of plastics, has recently been suggested to possibly cause **Parkinson**'s disease (PD). Herein, we revisited this issue by assessing the effect of Tinuvin 123 on dopaminergic neurons of the substantia nigra following its stereotaxic injection in the rat. Twenty-one days post unilateral stereotaxic injection of Tinuvin 123, systemic injection of both apomorphine and amphetamine caused rotations toward the side of the lesion in these rats. Tinuvin 123 produced a small to moderate dose-dependent reduction in striatal levels of dopamine and metabolites on the side of the lesion. This compound also produced dramatic cell loss in the substantia nigra on the side of the lesion. However, the loss of cells lacked the phenotypic specificity for tyrosine hydroxylase (TH)-positive neurons that is expected with a dopaminergic neurotoxin. Indeed, aside from a robust glial reaction, both TH-positive and glutamic acid dehydrogenase (**GAD**)-positive neurons were destroyed, and near the site of the injection, there was complete tissue destruction. This study indicates that, using this mode of injection, Tinuvin 123 exerts a dramatic tissue toxicity without any evidence of specificity for dopaminergic neurons. Thus, our data argues against a role for Tinuvin 123 as an environmental toxin causing a clinical condition characterized by the selective loss of dopaminergic neurons as seen in PD.

3/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10526106 20163688 PMID: 10701753
Phenotypical characterization of the neurons expressing the D1 and D2 dopamine receptors in the monkey striatum.
Aubert I; Ghorayeb I; Normand E; Bloch B
UMR CNRS 5541, Laboratoire d'Histologie-Embryologie, Universite V. Segalen, Bordeaux 2, France. iaubert@hippocrate.u-bordeaux2.fr
Journal of comparative neurology (UNITED STATES) Feb 28 2000, 418 (1) p22-32, ISSN 0021-9967 Journal Code: HUV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The striatum is regulated by dopaminergic inputs from the substantia nigra. Several anatomical studies using in situ hybridization have demonstrated that in rodents, dopamine D1 and D2 receptors are segregated into distinct striatal efferent populations: dopamine D1 receptor into gamma-aminobutyric acid (GABA)/substance P striatonigral neurons, and dopamine D2 receptor into GABA/enkephalin striatopallidal neurons. The existence of such a segregation has not been investigated in primates. Therefore, to quantify the efferent striatal GABAergic neurons in the adult Cynomolgus monkey, we detected **GAD67** mRNA expression while considering that only a minority of the GABAergic population is composed of interneurons. To characterize the peptidergic phenotype of the neurons expressing dopamine D1 or D2 receptors, we examined the mRNA coding for these receptors in the striatum at the cellular level using single- and double in situ hybridization with digoxigenin and 35S ribonucleotide probes. Double in situ hybridization demonstrated a high coexpression of

dopamine D1 receptor and substance P mRNAs (91-99%) as well as dopamine D2 receptor and preproenkephalin A mRNAs (96-99%) in medium-sized neurons throughout the nucleus caudatus, putamen, and nucleus accumbens. Only a small subpopulation (2-5%) of the neurons that contained dopamine D1 receptor mRNA also expressed dopamine D2 receptor mRNA in all regions. Large-sized neurons known to be cholinergic expressed D2R mRNA. However, within the nucleus basalis of Meynert, the large cholinergic neurons expressed D2R mRNA, but the neurons producing enkephalin expressed neither D1R nor D2R mRNA. These results demonstrate that the striatal organizational pattern of D1 and D2 receptor segregation in distinct neuronal populations described in rodent also exists in primate.

3/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10205068 99323773 PMID: 10397644
Recombinant adeno-associated virus (AAV) drives constitutive production of glutamate decarboxylase in neural cell lines.
Mi J; Chatterjee S; Wong KK; Forbes C; Lawless G; Tobin AJ
Department of Physiological Sciences, University of California, Los Angeles, USA.
Journal of neuroscience research (UNITED STATES) Jul 1 1999, 57 (1) p137-48, ISSN 0360-4012 Journal Code: KAC
Contract/Grant No.: NS22256, NS, NINDS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Many neurological disorders result directly or indirectly from the loss of inhibitory function. Engineering the production of GABA, an inhibitory neurotransmitter, may therefore be able at least partly to restore the lost inhibition seen in epilepsy, **Parkinson**'s disease, or Huntington's disease. In this article, we describe a set of recombinant adeno-associated viruses (AAVs) that can deliver cDNAs encoding the GABA-producing enzyme, glutamate decarboxylase (**GAD**), directly into neural cells. We have characterized these recombinant AAVs in several cell lines derived from the CNS. These recombinant AAVs effectively transduced all neural cell lines, although with different efficiencies. Transduction occurred in both proliferating and nonproliferating cells, but actively proliferating cell lines had approximately six times greater transduction efficiency than nonproliferating cells. Furthermore, these AAVs maintained long-term expression of **GAD** in an astrocytic cell line for at least seven passages. These recombinant AAVs are promising vehicles for investigating the potential therapeutic effects of GABA in animal models of epilepsy and neurodegenerative diseases.

3/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10198107 99334205 PMID: 10405733
Stereotactic radiosurgical pallidotomy and thalamotomy with the gamma knife: MR imaging findings with clinical correlation--preliminary experience.
Friedman DP; Goldman HW; Flanders AE; Gollomp SM; Curran WJ
Department of Radiology, Wills Eye Hospital, Philadelphia, PA, USA. friedm11@jeflin.tju.edu
Radiology (UNITED STATES) Jul 1999, 212 (1) p143-50, ISSN 0033-8419 Journal Code: QSH
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
PURPOSE: To evaluate the temporal evolution and appearance of a radiosurgical lesion at magnetic resonance (MR) imaging and the clinical response in patients undergoing stereotactic radiosurgical pallidotomy or

thalamotomy with the gamma knife. MATERIALS AND METHODS: Seventeen patients with medically refractory movement disorders underwent stereotactic radiosurgical pallidotomy (n = 2) or thalamotomy (n = 15). A single dose of 120-140 Gy was administered to a target in the globus pallidus interna or ventralis intermedius thalamic nucleus. Postprocedure **gadolinium** -enhanced MR imaging and clinical assessment were performed at 1 month and 3 months. RESULTS: At 3 months, the radiosurgical lesion most commonly (n = 11) appeared as a ring-enhancing focus 5 mm or less in diameter surrounded by vasogenic edema that extended less than 7 mm in radius beyond the target. Five patients had ring-enhancing lesions 7 mm or more in diameter; four of these developed symptomatic perilesional edema at 3 (n = 2) or 8 (n = 2) months after the procedure. Onset of therapeutic effect began approximately 4 weeks after treatment. In the 15 patients with tremor, there was a mean decline of 2.1 on the Tremor Rating Scale. CONCLUSION: Findings in this pilot study suggest that radiosurgical thalamotomy is a promising treatment for medically refractory tremor. Three-month follow-up MR studies show a ring-enhancing lesion surrounded by a variable amount of vasogenic edema. Visualization of the radiosurgical lesion and the clinical response are delayed compared to that with radio-frequency procedures.

3/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10142918 99013981 PMID: 9795182

Novel synthesis and release of GABA in cerebellar granule cell cultures after infection with defective herpes simplex virus vectors expressing glutamic acid decarboxylase.

New KC; Gale K; Martuza RL; Rabkin SD

Departments of Microbiology and Immunology, Georgetown University Medical Center, 3970 Reservoir Road NW, Washington, DC 20007, USA.

Brain research. Molecular brain research (NETHERLANDS) Oct 30 1998, 61 (1-2) p121-35, ISSN 0169-328X Journal Code: MBR

Contract/Grant No.: 2P30-CA-51008, CA, NCI; NS33342, NS, NINDS

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The inhibitory amino acid neurotransmitter gamma-aminobutyric acid (GABA) is synthesized from glutamate in a single step by the enzyme glutamatic acid decarboxylase (**GAD**). We sought to determine whether viral vectors containing **GAD** cDNA could be used to enhance synthesis and stimulation-evoked release of GABA in cultures of CNS neurons. For this purpose, we generated double-cassette defective herpes simplex virus (HSV) vectors that expressed one of the two **GAD** isoforms (**GAD65** or **GAD67**), and Escherichia coli LacZ. Infection of cerebellar granule cell (CGC) cultures with vectors containing **GAD** cDNA resulted in a significant increase in isoform-specific expression of **GAD**, synthesis of GABA, and stimulation-evoked GABA release. **GAD65** and **GAD67** vector-infected neurons exhibited a comparable profile of GABA levels, synthesis and release, as well as **GAD** protein distribution. In CGCs cultured for 6 days in vitro (DIV), GABA synthesized after vector-derived **GAD** expression was released by treatment with glutamate or veratridine, but only in a Ca2+-independent fashion. In more mature (10 DIV) cultures, both Ca2+-dependent, K+ depolarization-induced, as well as Ca2+-independent, veratridine-induced, GABA release was significantly enhanced by **GAD** vector infection. Treatment of CGCs with kainic acid, which destroys most of the GABAergic neurons (<1% remaining), did not prevent vector-derived expression of **GAD** nor synthesis of GABA. This suggests that defective HSV vector-derived **GAD** expression can be used to increase GABA synthesis and release in CNS tissue, even in the relative absence of GABAergic neurons. The use of such **GAD** vectors in the CNS has potential therapeutic value in neurologic disorders such as epilepsy, chronic pain, **Parkinson**'s and Huntington's disease. Copyright 1998 Elsevier Science B.V.

3/3,AB/11 (Item [redacted] from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09927428 98377612 PMID: 9711733
Sequential postoperative appearance of radiofrequency pallidotomy lesions on MRI.
Lim JY; De Salles AA
Division of Neurosurgery, University of California at Los Angeles, School of Medicine, USA.
Stereotactic and functional neurosurgery (SWITZERLAND) 1997, 69 (1-4 Pt 2) p46-53, ISSN 1011-6125 Journal Code: SFN
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We analyzed 10 radiofrequency (RF) lesions over time in 9 patients who had follow-up MRI 1 h to 43 weeks following stereotactic pallidotomies performed for medically intractable idiopathic **Parkinson**'s disease. Pallidotomies were performed under MRI guidance, microelectrode recording, and electrical stimulation with neurological monitoring. We compared the MRI taken within 1 h after surgery for each patient to their respective follow-up MRI to determine the changes in size and signal characteristics of RF lesions over time. The postoperative follow-up MRI of RF lesions roughly fell into 4 time periods: 1 h (n = 10), 2 months (n = 3), 6 months (n = 3), and 10 months (n = 4). The average volume (+/- SD, mm3) of these lesions at each phase were as follows: 1 h = 124.35 +/- 58.48; 2 months = 50.5 +/- 30.71; 6 months = 32.36 +/- 21.07; 10 months = 53.19 +/- 28.91. The steep decline in the size of the lesion stabilizes by the 2-month period. Thereafter, the lesion size at 6 and 10 months remains stable. Eventually, the center of coagulative necrosis completely disappears, and the lesions persists as a cystic cavity. The contrast uptake of these RF lesions appears to resolve by the 6-month period. Immediate postoperative images show strong enhancement with **gadolinium**. There is a lesser degree of enhancement at 2 months, and no appreciable enhancement by 6 months. Interestingly, the patients with better outcome tended to have larger RF lesions. However, this difference was not statistically significant.

3/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09848592 98358161 PMID: 9691191
Age-dependent neurobehavioral plasticity following forebrain dopamine depletions.
Bruno JP; Sandstrom MI; Arnold HM; Nelson CL
Department of Psychology and Neuroscience Program, Ohio State University, Columbus, OH 43210, USA. jpbruno+@osu.edu
Developmental neuroscience (SWITZERLAND) 1998, 20 (2-3) p164-79, ISSN 0378-5866 Journal Code: EC5
Contract/Grant No.: MH-19936, MH, NIMH; MH-49874, MH, NIMH; NS-18842, NS, NINDS
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed
The differential neurobehavioral effects of forebrain dopamine (DA) depletions in neonatal and adult rats are reviewed. In contrast to the severe and long-lasting **parkinsonian** sensorimotor deficits seen in rats sustaining large DA depletions as adults, rats comparably depleted as neonates are spared from these gross behavioral deficits. While DA released from residual striatal DA terminals remains necessary for the gradual recovery of sensorimotor function in rats lesioned as adults and the sparing from deficits in rats lesioned as neonates, the specific roles of D1- and D2-like receptors differ between the two age groups. Coactivation of striatal D1 and D2 receptors by residual DA is necessary for the

expression of sensorimotor behavior in rats depleted of DA as adults (and in intact rats) whereas activation of either D1 or D2 receptors is sufficient for these behaviors in rats depleted of DA as neonates. We discuss the D1/D2 modulation of several important markers for striatal transmission (acetylcholine release from interneurons, induction of c-fos, and the expression of **GAD65** mRNA in striatal efferents) as potential mechanisms underlying this striking age-dependent plasticity following forebrain DA depletions.

3/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09770219 98270462 PMID: 9609299
Gamma knife radiosurgery for thalamotomy in **parkinsonian** tremor: a five-year experience.
Duma CM; Jacques DB; Kopyov OV; Mark RJ; Copcutt B; Farokhi HK
The Neurosciences Institute and Department of Radiation Oncology, Good Samaritan Hospital, Los Angeles, California 90017, USA.
Journal of neurosurgery (UNITED STATES) Jun 1998, 88 (6) p1044-9, ISSN 0022-3085 Journal Code: JD3
Comment in J Neurosurg. 1998 Jun;88(6) 1121-2
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
OBJECT: Certain patients, for example, elderly high-risk surgical patients, may be unfit for radiofrequency thalamotomy to treat **parkinsonian** tremor. Some patients, when given the opportunity, may choose to avoid an invasive surgical procedure. The authors retrospectively reviewed their experience using gamma knife radiosurgery for thalamotomies in this patient subpopulation: 1) to determine the efficacy of the procedure; 2) to see if there is a dose-response relationship; 3) to review radiological findings of radiosurgical lesioning; and 4) to assess the risks of complications. METHODS: Radiosurgical nucleus ventralis intermedius thalamotomy using the gamma knife unit was performed to make 38 lesions in 24 men and 10 women (median age 73 years, range 58-87 years) over a 5-year period. A median radiation dose of 130 Gy (range 100-165 Gy) was delivered to 38 nuclei (four patients underwent bilateral thalamotomy) using a single 4-mm collimator following classic anatomical landmarks. Twenty-nine lesions were made in the left nucleus ventralis intermedius thalamus for right-sided tremor. Patients were followed for a median of 28 months (range 6-58 months). Independent neurological evaluation of tremor based on the change in the Unified **Parkinson**'s Disease Rating Scale tremor score was correlated with subjective patient evaluation. Comparison was made between a subgroup of patients in whom "low-dose" lesions were made (range 110-135 Gy, mean 120 Gy) and those in whom "high-dose" lesions were made (range 140-165 Gy, mean 160 Gy) for purposes of dose-response information. Four thalamotomies (10.5%) failed, four (10.5%) produced mild improvement, 11 (29%) produced good improvement, and 10 (26%) produced excellent relief of tremor. In nine thalamotomies (24%) the tremor was eliminated completely. The median time to onset of improvement was 2 months (range 1 week-8 months). Concordance between an independent neurologist's evaluation and that of the patient was statistically significant ($p < 0.001$). Two patients who underwent unilateral thalamotomy experienced bilateral improvement in their tremor. There were no neurological complications. There was better tremor reduction in the high-dose group than in the low-dose group ($p < 0.04$). CONCLUSIONS: Although less effective than other stereotactic techniques, gamma knife radiosurgery for thalamotomy offers tremor control with minimal risk to patients unsuited for open surgery.

3/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

gadolinium -enhanced magnetic resonance (MR) images of 56 patients treated for **parkinsonism**, pain, or other functional diseases were used to measure 140 lesion sizes at various times after radiosurgical treatment (1-26 months, mean: 11.3 months). Only the 4-mm collimator was used to create the lesions. The maximum dose ranged from 110 to 180 Gy (mean: 145 Gy). In 42 cases (78%), one isocenter was used to create the lesion. Thirteen lesions (20%) were created with two isocenters and in 1 case, three isocenters were used. Lesions were detectable on MR images as early as 30 days after treatment. The maximum lesion volume was reached after 6-12 months and ranged from nondetectable to more than 4,000 mm3. Larger lesion volumes were strongly associated with the use of more than one isocenter. In addition, maximum doses of 160 Gy or more increased the likelihood of producing lesions larger than expected. It is therefore concluded that the use of the Gamma Knife for the treatment of functional disorders is safest when single-isocenter shots with the 4-mm collimator and a maximum dose of less than 160 Gy are used.

3/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09074572 97085452 PMID: 8931592
Subthalamotomy in **parkinsonian** monkeys. Behavioural and biochemical analysis.
Guridi J; Herrero MT; Luquin MR; Guillen J; Ruberg M; Laguna J; Vila M; Javoy-Agid F; Agid Y; Hirsch E; Obeso JA
Department of Neurosurgery, Hospital de Navarra, Spain.
Brain; a journal of neurology (ENGLAND) Oct 1996, 119 (Pt 5) p1717-27, ISSN 0006-8950 Journal Code: B5F
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Nineteen Macaca fascicularis monkeys were divided into four different groups: Group A (n = 3), control; Group B (n = 3), monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP); Group C (n = 8), animals treated with MPTP in which the subthalamic nucleus (STN) was unilaterally lesioned by kainic acid injection; in Group D (n = 5), the STN was lesioned prior to MPTP administration. Subthalamotomy resulted in a bilateral improvement of tremor, spontaneous activity, bradykinesia (evaluated by a manual motor test) and freezing in Group C. All these monkeys developed hemichorea contralateral to the lesion. The improvement was maintained and the hemichorea continued until death. The monkeys in group D showed severe hemiballism which persisted throughout MPTP administration and developed **parkinsonian** signs mainly on the side ipsilateral to the lesion. Analysis of the in situ hybridization of the mRNA coding for glutamic acid decarboxylase (**GAD**) of MPTP monkeys showed a significant increase in the mean density of silver grains over every labelled neuron in the globus pallidum lateralis (56.8% over control) as well as the globus pallidus medialis (GPM) (45.7% over control) and the substantia nigra reticulata (SNR) (35.8% over control). No significant change was observed in the thalamic nucleus reticularis. Subthalamotomy (Groups C and D) produced a significant reduction in mRNA **GAD** expression on the side of the lesion in the GPM and the SNR (34% and 42.3%, respectively) with respect to the ipsilateral (non-lesioned) side and also when compared with **parkinsonian** monkeys. These results confirm and expand, at the cellular level, the paramount role of STN hyperactivity in the pathophysiology of **parkinsonism**. The therapeutic consequences of these findings for surgical treatment of **Parkinson**'s disease are discussed.

3/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08911415 96173696 PMID: 8618687

3/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08856805 94270766 PMID: 8210225
MRI detects acute degeneration of the nigrostriatal dopamine system after MPTP exposure in hemiparkinsonian monkeys.
Miletich RS; Bankiewicz KS; Quarantelli M; Plunkett RJ; Frank J; Kopin IJ ; Di Chiro G
Neuroimaging Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892.
Annals of neurology (UNITED STATES) Jun 1994, 35 (6) p689-97, ISSN 0364-5134 Journal Code: 6AE
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can cause an acute chemical toxicity resulting in a **parkinsonian** state in humans and nonhuman primates. We wished to assess whether the toxicity from MPTP is associated with changes on magnetic resonance images of brain structures containing dopamine neuronal processes or with disruption of the blood-brain barrier. Normal rhesus monkeys and monkeys at various times after being subjected to unilateral intracarotid injection of MPTP (0.4 mg/kg) were studied with magnetic resonance imaging using T1- and T2-weighted spin-echo and gradient-echo sequences. Disruption of the blood-brain barrier was assessed also with magnetic resonance imaging after administration of **gadolinium**-diethylenetriamine pentaacetic acid. **Parkinsonian** symptoms contralateral to the infused carotid usually appeared within 1 day after MPTP exposure, reaching their peak severity by 7 days, when all monkeys showed clear clinical abnormalities. Magnetic resonance imaging changes developed in concomitance with the clinical signs and were characterized by increased signal intensity on T2-weighted images as well as decreased intensity on T1-weighted images of the ipsilateral caudate and putamen. T2 hyperintensity was also present just dorsal to the pars compacta of the substantia nigra, in the region of the proximal nigrostriatal tract. All magnetic resonance imaging changes dissipated in the next 2 weeks. There were no abnormalities at any time in the globus pallidus, nucleus accumbens, and other structures innervated by the mesocorticolimbic dopamine system. After MPTP exposure, there was no evidence of blood-brain barrier disruption, suggesting that vasogenic edema was an unlikely factor in the production of the observed abnormalities.(ABSTRACT TRUNCATED AT 250 WORDS)

3/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08130[illegible] 98493 PMID [illegible]

[illegible] surgery for **Parkinson** disease.
[illegible] Lufkin RB
[illegible]e Health Sciences
[illegible]ED STATES) Ja[illegible] 4
[illegible]O

both rodent and primate models; however, uncertain consequences of long-term growth factor expression and question regarding timing of therapy in the disease course must be resolved before any clinical study can be contemplated. We now propose to infuse into the subthalamic nucleus (STN) recombinant AAV vectors expressing the two isoforms of the enzyme glutamic acid decarboxylase (**GAD**-65 and **GAD**-67), which synthesizes the major inhibitory neurotransmitter in the brain, GABA. The STN is a very small nucleus (140 cubic mm or 0.02% of the total brain volume, consisting of approximately 300,000 neurons) which is disinhibited in PD, leading to pathological excitation of its targets, the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNpr). Increased GPi/SNpr outflow is believed responsible for many of the cardinal symptoms of PD, i.e., tremor, rigidity, bradykinesia, and gait disturbance. A large amount of data based on lesioning, electrical stimulation, and local drug infusion studies with GABA-agonists in human PD patients have reinforced this circuit model of PD and the central role of the STN. Moreover, the closest conventional surgical intervention to our proposal, deep brain stimulation (DBS) of the STN, has shown remarkable efficacy in even late stage PD, unlike the early failures associated with recombinant GDNF infusion or cell transplantation approaches in PD. We believe that our gene transfer strategy will not only palliate symptoms by inhibiting STN activity, as with DBS, but we also have evidence that the vector converts excitatory STN projections to inhibitory projections. This additional dampening of outflow GPi/SNpr outflow may provide an additional advantage over DBS. Moreover, of perhaps the greatest interest, our preclinical data suggests that this strategy may also be neuroprotective, so this therapy may slow the degeneration of dopaminergic neurons. We will use both **GAD** isoforms since both are typically expressed in inhibitory neurons in the brain, and our data suggest that the combination of both isoforms is likely to be most beneficial. Our preclinical data includes three model systems: (1) old, chronically lesioned **parkinsonian** rats in which intraSTN **GAD** gene transfer results not only in improvement in both drug-induced asymmetrical behavior (apomorphine symmetrical rotations), but also in spontaneous behaviors. In our second model, **GAD** gene transfer precedes the generation of a dopamine lesion. Here **GAD** gene transfer showed remarkable neuroprotection. Finally, we carried out a study where **GAD**-65 and **GAD** -67 were used separately in monkeys that were resistant to MPTP lesioning and hence showed minimal symptomatology. Nevertheless **GAD** gene transfer showed no adverse effects and small improvements in both **Parkinson** rating scales and activity measures were obtained. In the proposed clinical trial, all patients will have met criteria for and will have given consent for STN DBS elective surgery. Twenty patients will all receive DBS electrodes, but in addition they will be randomized into two groups, to receive either a solution containing rAAV-**GAD** , or a solution which consists just of the vector vehicle, physiological saline. Patients, care providers, and physicians will be blind as to which solution any o

3/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11519502 21379315 PMID: 11487201
Alterations in **GAD67** , dynorphin and enkephalin mRNA in striatal output neurons following priming in the 6-OHDA model of **Parkinson**'s disease.
Carta A; Fenu S; Morelli M
Department of Toxicology, University of Cagliari, Italy.
Neurological sciences (Italy) Feb 2001, 22 (1) p59-60, ISSN 1590-1874 Journal Code: DRB
Languages: ENGLISH
Document type: Journal Article
Record type: In Process
In the 6-hydroxydopamine (6-OHDA) rat model of **Parkinson**'s disease, administration of a dopaminergic agonist sensitizes rats to a subsequent

nor high signal intensity on T2-weighted images was evident within the caudate head. The one patient studied after administration of **gadopentetate** dimeglumine showed no abnormal enhancement. These images provided a description of the transplant site and also suggested that the clinical improvement seen was not due to simple ablation of caudate tissue or to postoperative inflammation. The increase in size of the caudate head also suggested that some implanted tissue may have remained in these patients at the time the MR images were acquired.

3/3,AB/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08001381 93137245 PMID: 8093682
An animal model for coexisting tardive dyskinesia and tardive **parkinsonism**: a glutamate hypothesis for tardive dyskinesia.
Gunne LM; Andren PE
Department of Psychiatry, Ulleraker, Uppsala University, Sweden.
Clinical neuropharmacology (UNITED STATES) Feb 1993, 16 (1) p90-5, ISSN 0362-5664 Journal Code: CNK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
There is now ample evidence for long-term malfunctioning within five different brain GABAergic pathways in a monkey model for tardive dyskinesia (TD). Three of these GABA connections (GPe-STN, CP-SNr, and CP-GPi) are chronically downregulated during neuroleptic treatment and after some years they do not seem to regain their normal activity, even when the neuroleptics are discontinued. The persistent downregulation of these three GABA connections, evidenced by depressions of terminal **GAD** activity and GABA levels, appears to be a conceivable mechanism behind tardive **parkinsonism** (TP), often reported to coexist with TD in the clinic. The TD patients' well-known lack of awareness of their symptoms may be due to their **parkinsonian** "sensory neglect." Another two GABA malfunctioning connections were found in our monkey model: SNr-VA/VL and GPi-VA/VL. These pathways are upregulated during chronic neuroleptic treatment, partly due to an elevated glutamate release within subthalamofugal pathways. This chronic glutamatergic hyperactivity may have acted via an excitotoxic mechanism and consequently both GPi and VA/VL had a low synaptic activity in our dyskinetic monkeys, as measured by 2-deoxyglucose uptake, even 4 months after the last neuroleptic dose. It is hypothesized that TD may be due to an excitotoxic lesion of the inhibitory GABAergic VA/VL afferents, while TP has to do with persistent malfunctioning of downregulated SNr and GPi afferents.

3/3,AB/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07987589 94105401 PMID: 8278600
Dopaminergic regulation of glutamic acid decarboxylase mRNA expression and GABA release in the striatum: a review.
Lindefors N
Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden.
Progress in neuro-psychopharmacology & biological psychiatry (ENGLAND) Nov 1993, 17 (6) p887-903, ISSN 0278-5846 Journal Code: Q45
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed
1. The majority of neurons in the striatum (caudate-putamen, dorsal striatum; nucleus accumbens, ventral striatum) and in striatal projection regions (the pallidum, the entopeduncular nucleus and substantia nigra reticulata) use gamma-aminobutyric acid (GABA) as transmitter and express glutamic acid decarboxylase (**GAD** ; rate limiting enzyme) in the synthesis of GABA. GABA is the major inhibitory transmitter in the

mammalian brain. 2. **GAD** in brain is present as two isoenzymes, **GAD65** and **GAD67**. **GAD65** is largely present as an inactive apoenzyme, which can be induced by nerve activity, while most **GAD67** is present as a pyridoxal phosphate-bound permanently active holoenzyme. Thus **GAD65** and **GAD67** seem to provide a dual system for the control of neuronal GABA synthesis. 3. **GAD** mRNA expression can be visualised and quantified using in situ hybridisation, and GABA release can be quantified using in vivo microdialysis. 4. Different populations of GABA neurons can be distinguished in both dorsal and ventral striatum as well as in other parts of the basal ganglia. 5. Inhibition of dopaminergic transmission in the striatum by lesion of dopamine neurons or by neuroleptic treatment is followed by an increased release of GABA and increased expression of **GAD67** mRNA in a subpopulation of striatal medium-sized neurons which project to the globus pallidus, and increased striatal **GAD** enzyme activity. 6. Increased dopaminergic transmission by repeated but not single doses of amphetamine is followed by decreased striatal GABA release and decreased **GAD67** mRNA expression in a subpopulation of medium-sized neurons in the striatum. 7. Two populations of medium-sized GABA neurons in the striatum seem to be under tonic dopaminergic influence. The majority of these GABA neurons are under inhibitory influence, whereas a small number seem to be stimulated by dopamine. 8. Specific changes in activity in subpopulations of striatal GABA neurons probably mediate the dopamine-dependent hypokinetic syndrome seen in **Parkinson**'s disease and following neuroleptic treatment.

3/3,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05986319 86014881 PMID: 4047404
Gamma-aminobutyric acid (GABA) levels and glutamate decarboxylase (**GAD**) activity of the brain of rats with extrapyramidal syndrome after acute manganese chloride poisoning]
Poziom kwasu gamma-aminomaslowego (GABA) oraz aktywnosc dekarboksylazy glutaminianowej (**GAD**) w mozgu szczura z zespolem pozapiramidowym po ostrym zatruciu chlorkiem manganawym.
Kosicka B; Bugera TE; Kittel M; Smialek M
Neuropatologia polska (POLAND) 1985, 23 (2) p191-200, ISSN 0028-3894 Journal Code: NZ5
Languages: POLISH
Document type: Journal Article
Record type: Completed

3/3,AB/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05927577 89126142 PMID: 2851679
GABAA receptor but not muscarinic receptor density was decreased in the brain of patients with **Parkinson**'s disease.
Nishino N; Fujiwara H; Noguchi-Kuno SA; Tanaka C
Department of Pharmacology, Kobe University School of Medicine, Japan.
Japanese journal of pharmacology (JAPAN) Nov 1988, 48 (3) p331-9, ISSN 0021-5198 Journal Code: KO7
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The activity of glutamic acid decarboxylase (**GAD**) and choline acetyltransferase (ChAT) as presynaptic markers of gamma-aminobutyric acid (GABA)- and acetylcholine (ACh)-containing neurons, and the binding of [3H]muscimol and [3H]quinuclidinyl benzilate ([3H]QNB) as postsynaptic ones were measured in autopsied samples of the caudate nucleus, putamen, pallidum, substantia nigra and the cerebral cortex from L-dopa-treated patients with Stage V (terminally bedridden) patients with **Parkinson**'s Disease (PD). In PD, **GAD** activities were significantly reduced in

the caudate nucleus and substantia nigra relative to normal controls, but were normal when the values from protracted terminal illness (PTI) cases were used as the controls. ChAT activities were reduced in all regions studied. These reductions in **GAD** and ChAT activities were not accompanied by a concomitant increase in the density of GABAA or muscarinic receptors. GABAA receptor densities were significantly decreased in both the cortical and subcortical brain regions, while muscarinic receptor densities remained unchanged. We suggest that the decreased density of GABAA receptor in PD brains reflects degeneration of neurons on which the receptor is localized, i.e., degeneration of ascending monoaminergic neurons including nigral dopamine (DA) neurons.

3/3,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05863848 85184829 PMID: 4039359
Brain glutamate decarboxylase and cholinergic enzyme activities in scrapie.
Iqbal K; Somerville RA; Thompson CH; Wisniewski HM
Journal of the neurological sciences (NETHERLANDS) Mar 1985, 67 (3) p345-50, ISSN 0022-510X Journal Code: JBJ
Contract/Grant No.: NS-17487, NS, NINDS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
C57BL/6J mice, age 6-8 weeks were inoculated intracerebrally with brain homogenate from mice previously infected with the 139A strain of scrapie; control mice were identically treated with brain homogenate from non-infected normal mice. The activities of choline acetyltransferase (CAT), acetyl cholinesterase (AChE), and glutamic acid decarboxylase (**GAD**) were determined in the forebrain and hindbrain of these animals after 67, 126 and 151 days post-inoculation. There were no significant differences in the activities of CAT and **GAD** between scrapie and control mice at early, middle or late stages of the disease in the scrapie-infected animals; there was an about 20% decline in AChE activity in the scrapie brain.

3/3,AB/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05554110 89010768 PMID: 2459307
Similar time course changes in striatal levels of glutamic acid decarboxylase and proenkephalin mRNA following dopaminergic deafferentation in the rat.
Vernier P; Julien JF; Rataboul P; Fourrier O; Feuerstein C; Mallet J
Departement de Genetique Moleculaire, Centre National de la Recherche Scientifique, Gif-sur-Yvette, France.
Journal of neurochemistry (UNITED STATES) Nov 1988, 51 (5) p1375-80, ISSN 0022-3042 Journal Code: JAV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The time course changes in levels of mRNA encoding glutamic acid decarboxylase (**GAD**) and proenkephalin (PPE) was analyzed in the rat striatum following unilateral lesion of substantia nigra with 6-hydroxydopamine. The levels of both **GAD** and PPE mRNAs increased after the dopaminergic deafferentation, reaching concomitantly a maximal twofold increase on day 25. Thereafter, the mRNA levels declined; at 4 months, the amount of PPE mRNA remained slightly elevated whereas **GAD** mRNA had returned to the control value, suggesting the action of a compensatory mechanism. We also observed a rise of glial fibrillary acidic protein mRNA level which reflects a reactive astrocytosis. In contrast, alpha-tubulin mRNA level remained unchanged, indicating that no significant

synaptogenesis occurs in this experimental situation. No obvious modification in mRNA levels was detected in the striatum contralateral to the lesion. These results highlight the role of the modulation of gene expression in adaptive processes to dopamine deficiency in striatal efferent pathways. Its relevance to the pathophysiology of **Parkinson**'s disease is discussed.

3/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04936192 85227304 PMID: 4005526
Brain glutamate decarboxylase in **Parkinson**'s disease with particular reference to a premortem severity index.
Monfort JC; Javoy-Agid F; Hauw JJ; Dubois B; Agid Y
Brain; a journal of neurology (ENGLAND) Jun 1985, 108 (Pt 2) p301-13, ISSN 0006-8950 Journal Code: B5F
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Glutamate decarboxylase (**GAD**) activity was estimated in various areas of the brain in 21 control and 26 **parkinsonian** subjects matched for age, postmortem delay and premortem state. Retrospective analysis of clinical data was used to define a premortem severity index (PMSI), scaled from 0 to 6, based upon a semiquantitative estimation of the duration of anoxia (0-3) and hypovolaemia (0-3). A significant correlation was found between **GAD** activity and PMSI in most regions of the brain. In the prefrontal cortex and caudate nucleus, **GAD** activity was not correlated with age, postmortem delay, sepsis, being bedridden, or with cachexia. Dosage and duration of drug treatment did not influence striatal or cortical **GAD** levels. In **Parkinson**'s disease, **GAD** activity did not differ from controls in many brain areas except in the caudate nucleus, hippocampus and the frontal and occipital cortex. No difference in striatal and cortical **GAD** activity was observed when 10 control and 9 **parkinsonian** brains were selected for an optimal premortem state which approximated to sudden death (PMSI less than or equal to 2). **GAD** activity in the caudate nucleus and prefrontal cortex was not significantly influenced by the duration of L-DOPA treatment or withdrawal, disease duration, or severity of intellectual deterioration. Although the number of samples in certain brain areas was too small to allow a definitive conclusion, these results make it doubtful that GABAergic neurons are damaged in this disease.

3/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04904851 84128155 PMID: 6667289
Topographic and chemical study of the GABA synthetizing enzyme in **Parkinsonian** syndromes]
Etude topographique et chimique de l'enzyme de synthese du GABA dans les syndromes **parkinsoniens**.
Kopp N; Jordan D; Michel JP; Pialat J; Veisseire M; Chazot G; Tommasi M
Annales de pathologie (FRANCE) Dec 1983, 3 (4) p327-31, ISSN 0242-6498 Journal Code: AAZ
Languages: FRENCH
Document type: Journal Article
Record type: Completed
After a classical neuropathological study assessing the diagnosis, the activity of the GABA synthetizing enzyme, glutamate decarboxylase (**GAD**), was assayed in 6 brain areas, in 8 cases of **Parkinson**'s disease, 2 cases of idiopathic orthostatic hypotension and 9 control cases carefully matched. The activity of **GAD** is not impaired, as classically believed, in **parkinsonian** brains, particularly in substantia nigra and pallidum. This preservation would indicate the absence

of lesion of GABAergic neurones in **Parkinson**'s disease. In the cases of other **Parkinsonian** syndromes, the number of cases studied is too limited to allow any generality; but they are, however reported because of their rarity.

3/3,AB/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04877114 84204795 PMID: 6144364
Substantia nigra cell death from kainic acid or folic acid injections into the pontine tegmentum.
McGeer EG; McGeer PL
Brain research (NETHERLANDS) Apr 30 1984, 298 (2) p339-42, ISSN 0006-8993 Journal Code: B5L
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Injections of kainic acid into the rostral pontine tegmentum in rats caused not only local lesions but destruction of GABAergic and dopaminergic cells in the substantia nigra (SN), as indicated histologically and by measurements of tyrosine hydroxylase (TH) and glutamate decarboxylase (**GAD**). Injections of folic acid caused the nigral damage without local lesions. Pretreatment with scopolamine prevented the losses in **GAD** without affecting those in TH. The destruction of nigral cells is attributed to pathological stimulation of afferent pathways to the SN, some of which are cholinergic, and it is possible that a similar mechanism may be involved in some forms of **Parkinsonism**.

3/3,AB/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04849946 82054780 PMID: 6117604
Microtopography of tyrosine hydroxylase, glutamic acid decarboxylase, and choline acetyltransferase in the substantia nigra and ventral tegmental area of control and **Parkinsonian** brains.
Javoy-Agid F; Ploska A; Agid Y
Journal of neurochemistry (UNITED STATES) Nov 1981, 37 (5) p1218-27, ISSN 0022-3042 Journal Code: JAV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Tyrosine hydroxylase (TH), glutamic acid decarboxylase (**GAD**), and choline acetyl transferase (CAT) were used as markers for catecholamine, gamma-aminobutyric acid, and acetylcholine containing neurons in human mesencephalon. Their rostrocaudal, mediolateral, and dorsoventral distribution was investigated within the substantia nigra pars compacta (SNC) and pars reticulata (SNR) and in the ventral tegmental area (VTA). TH activity was highest in the caudal, medial, and ventral SNC and in the middle of VTA medio-ventrally. The enzyme activity in SNR was low and uniformly distributed. In SNC as well as SNR, **GAD** activity was high and greater laterally and in the middle of the rostro-caudal extent. No particular pattern of distribution was observed in VTA. an area with low **GAD** content. In the substantia nigra, CAT activity was low. A characteristic medio-ventral distribution with a peak of high enzyme activity in the middle of the rostrocaudal extent was observed. In VTA, enzyme levels were high and also concentrated medio-ventrally and in the middle of the area. In **parkinsonian** brains, the distribution of TH was uniformly affected throughout the rostro-caudal extent. In VTA the enzyme activity was not as reduced as in SNC and SNR; the CAT pattern was only disrupted in a very localized part of SNC but not in SNR and VTA. In all three areas, **GAD** activity was reduced to a uniformly low distribution.